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TREATMENT OF SCARLET FEVER

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During the past twenty years the treatment of scarlet fever has been radically changed by new technics which have become available. Three types of therapy are now possible: (1) chemotherapy with sulfonamide compounds; (2) administration of commercial antitoxin, and (3) administration of convalescent serum. An analysis of these various therapeutic measures is pertinent if the serious effects of this disease are to be combated successfully.

In 1940, Fox and Hardgrove [1] compared azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′ - hydroxynaphthalene-3′,6′-disulfonate) with convalescent serum for the therapy of scarlet fever. It was demonstrated that this sulfonamide compound had no appreciable effect on the syndrome caused by the erythrogenic toxin, whereas the convalescent serum produced an immediate response. Azosulfamide was of value in treating specific complications, such as streptococcemia, meningitis and surgically inaccessible foci but was of no value for the toxic phase or type of the disease. French [2] noted similar results in a well controlled series of patients treated with and without sulfanilamide. He stated that the ". . . sulfanilamide had no significant effect upon the initial symptoms of scarlet fever, or upon the kind, incidence or duration of later complications." The National Research Council Committee in 1941 [3] also inferred that sulfanilamide has no effect on the toxic stage of the disease, since it advised that sulfanilamide in simple toxic scarlet fever ". . . should be used for prophylaxis of septic complication . . ." and in toxic and septic scarlet fever is ". . . recommended in addition to antitoxin for its chemotherapeutic effect on septic lesions." Wesselhoeft [4] stated the belief that the incidence of complications would be lessened by administration of sufficiently large doses of sulfanilamide at the onset of the disease and continuing use of the drug for three weeks. He pointed out, however, that the administration of sulfanilamide for so long a period necessarily requires that a patient be transferred from his home to a hospital, where impending signs of toxicity due to the drug can be closely observed. Because of the agreement in opinions which have just been cited, the use of sulfonamide compounds for uncomplicated scarlet fever has been abandoned at the South View Hospital of the City of Milwaukee Health Department.

The value of commercial antitoxin is well recognized as a means of combating the toxic effects of scarlet fever, but its use introduces the danger of foreign protein reactions. The incidence of reactions to human and animal serums was discussed by Fox [5] in 1937.

In a preliminary report on the use of pooled human convalescent serum, Fox and Hardgrove [6] compared results for 589 patients treated with serum in contrast to those for 139 patients treated with commercial antitoxin and 300 patients receiving general symptomatic therapy. They found that the use of serum lessened complications, decreased the mortality rate, shortened the period of pyrexia and commonly improved

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1. Fox, M., and Hardgrove, M.: Scarlet Fever Therapy: A Comparison of Convalescent Serum and Sulphanilamide, Am. J. M. Sc. **199**:495 (April) 1940.

2. French, J. O.: The Sulphanilamide Treatment of Scarlet Fever, J. Hyg. **39**:581 (Sept.) 1939.

3. Chemotherapy for Infectious Diseases and Other Infections, Circular Letter no. 81, Committee on Chemotherapeutic and Other Agents and Subcommittee on Infectious Diseases of Division of Medical Sciences, National Research Council, War Med. **1**:55 (Jan.) 1941.

4. Wesselhoeft, C.: The Treatment of Diphtheria and Scarlet Fever, M. Clin. North America **25**:1273 (Sept.) 1941.

5. Fox, M. J.: Relation of Incidence of Human and Animal Serum Disease, J. Infect. Dis. **61**:341 (Nov.-Dec.) 1937.

6. Fox, M., and Hardgrove, M.: Therapeutic Value of Convalescent Serum in Scarlet Fever, Arch. Int. Med. **60**:494 (Sept.) 1937.

symptoms. Significantly, they did not encounter untoward reactions following the use of the human convalescent serum. Their conclusions substantiated the results obtained by Thalhimer and Levinson.[7]

In preparing the present paper we reviewed the cases of all of the patients with scarlet fever who had been interned at the South View Hospital during the past six years (1937 to 1943). These patients totaled 7,500. Of this number, 1,000 had received pooled human convalescent serum. In order to evaluate the effect of this serum therapy, 1,000 consecutive cases were chosen from the hospital records for comparison. These control cases were deliberately selected from the year 1923, when only symptomatic treatment could be used, since antitoxin, convalescent serum and sulfonamide compounds were not then available.

TABLE 1.—*Classification and Incidence of Cases*

Clinical Type	Incidence: Controls	Incidence: Serum Treated	Signs and Symptoms	Complications
Mild				
Without rash..	235	0	Angina; nausea and vomiting; slight fever	Rhinorrhea; perlèche; slight cervical adenitis
With rash.....	562	114		
Toxic.....	187	764	High fever; prostration; marked nausea and vomiting; lethargy; mania; diffuse rash	
Septic.....	12	73	.....	Otitis media; sinusitis; meningitis; mastoiditis; cellulitis; peritonsillar abscess; paronychia; streptococcemia
Toxic and septic.	0	46		
Malignant.....	4	3	Severe signs and symptoms; purpuric rash	Endocarditis; septicemia; meningitis; encephalitis

Before discussing the details of comparison between these two groups of cases, we should emphasize that the series of 1,000 patients of 1937 to 1943 contained a far higher percentage of seriously ill persons than did the 1,000 patients of 1923. The majority of the patients treated with convalescent serum from 1937 to 1943 were sufficiently ill to justify the use of the serum, whereas the 1923 patients chosen included merely consecutively admitted patients with scarlet fever. The results which we are about to report are all the more outstanding because of this difference in the two series. We are not including at this time a discussion of the cases of the remaining 6,500 patients admitted from 1937 to 1943, since all of these patients were less seriously ill than the serum-treated patients and would therefore not be reliable as a comparable group for evaluating the results obtained in the latter patients.

In table 1 the two series of cases are analyzed and compared on the basis of signs and symptoms for the various clinical types and complications of scarlet fever. Six categories have been devised for grading the severity of the disease. It is evident that 88.6 per cent of the patients treated with serum were severely ill, in contrast to only 20.3 per cent of the control series. This inverse ratio between the two series for the severity of the disease should be kept in mind when noting the morbidity-mortality percentages and the incidence of complications.

TABLE 2.—*Morbidity and Mortality*

	Controls	Serum-Treated
Pyrexia—mean days of duration.....	5.5	2.1
Duration of disease—mean days.....	43.5	24.5
Deaths—number.....	20	17

TABLE 3.—*Complications in Patients Treated With and Without Serum*

Complication	Controls Treated Without Serum	Convalescent Serum Series: Present at Onset or Before Serum Given	Convalescent Serum Series: Persisting 5 Days After Treatment	Convalescent Serum Series: Developing After Serum Given
Cervical adenitis.....	380	733	243	20
Rhinorrhea.....	207	263	14	12
Otitis media.....	91	175	98	35
Suppurative adenitis.....	4	1	1	2
Small bone synovitis.....	7	69	7	12
Mastoiditis.....	9	9	5	2
Nephritis.....	12	5	5	7
Ethmoid sinusitis.....	0	14	2	4
Peritonsillar abscess.....	7	10	4	15
Peritonsillitis.....	0	5	5	2
Pneumonia.....	0	7	7	2
Septicemia.....	9	1	1	1
Meningitis.....	1	2	1	0
Surgical scarlet fever.....	11	25	0	0
Perlèche.....	14	139	30	2
Erysipelas.....	0	2	2	3
Recrudescence.....	0	19	0	5

In table 2 are presented the morbidity-mortality statistics for the two series. It will be observed that the average duration of pyrexia for the serum-treated patients was only two and one-tenth days, while in the control group pyrexia lasted an average of five and five-tenths days, although the conditions were milder. It is also notable that the serum-treated patients had a mean duration of disease of only twenty-four and five-tenths days, in contrast to the mean duration of forty-three and five-tenths days for the control series. Although the patients receiv-

7. Thalhimer, W., and Levinson, S. O.: Pooled Convalescent Scarlet Fever Treatment of Diverse Streptococcic Infections, J. A. M. A. **105**:864 (Sept. 14) 1935.

ing the serum were more seriously ill, only seventeen deaths occurred, whereas there were twenty fatalities in the control group.

The complications which occurred frequently are listed in table 3. Many of these complications were present when the patients were brought to the hospital. Table 3 indicates whether the complications persisted more than five days after the serum treatment was initiated

TABLE 4.—*Type of Response to Serum Treatment in Various Age Groups*

Age Group	Total Number of Cases	Satisfactory Response to First Dose		Satisfactory Response to Second Dose		Unsatisfactory Response to Serum Therapy	
		No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent
0 - 5	263	188	71.48	37	14.07	38	14.44
6 - 10	286	246	86.01	21	7.34	19	6.64
11 - 15	140	115	82.14	10	7.14	15	10.71
16 - 20	96	83	86.45	3	3.12	10	10.41
21 - 30	126	114	90.47	8	6.34	4	3.17
31 - 40	63	59	93.49	3	4.76	1	1.58
41 - 50	18	18	100.00	0	0.0	0	0.0
51 - 60	5	5	100.00	0	0.0	0	0.0
Over 61	3	2	66.67	0	0.0	1	33.33
Totals for all ages	1,000	830	83.0	82	8.2	88	8.8

or whether the complications developed after the serum was given. It is significant that the results recorded in this table emphasize the serious condition of the serum-treated patients. Our previous comment should also be remembered, that with many of the complications, such as these, sulfonamide compounds form a valuable adjunct to therapy with convalescent serum.

TABLE 5.—*Doses of Human Convalescent Serum*

	Previous Doses,* Cc.	Present Doses,† Cc.
Infants:		
Moderate	20	10-20
Severe	20-40	20-40
Children:		
Moderate	20-40	20-30
Severe	60	30-60
Adults:		
Moderate	40- 60	20-40
Severe	80-100	40-80

* From Fox.[8]
† Used in later years of present study.

Table 4 shows the type of response to serum treatment in the various age groups. The table is self explanatory. Of the patients studied, 83 per cent showed rapid clinical improvement of the rash and the sore throat; 8.2 per cent required an additional dose of serum; 8.8 per cent failed to benefit from the serum therapy.

During these six years of use of pooled human convalescent serum for the treatment of scarlet fever, the dosage of serum advisable has been revised. In table 5 are listed the doses recommended by Fox,[8] in 1940 and the doses which were used during the later years of this study. It was found that smaller doses proved to be as effective as the former larger doses and were especially efficacious if the patient received the serum early in the course of the disease.

SUMMARY

Three types of therapy for scarlet fever have been evaluated through review of literature and analysis of results in patients with scarlet fever interned at the South View Hospital. Two series of 1,000 cases each have been studied for the present report.

Sulfonamide compounds find their chief value in the treatment of certain complications. These drugs are of no value in the management of the toxic phase or type of scarlet fever.

The use of commercial antitoxin, prepared with horse serum, combats the toxic phase of the disease but introduces the danger of foreign protein reactions.

Pooled human convalescent serum produces rapid clinical response when administered to patients with scarlet fever and offers the best means of therapy. Notable beneficial effects of its use include the following: prompt subsidence of fever, alleviation of signs and symptoms, avoidance or improvement of complications (with certain exceptions cited), shortened period of hospitalization and lower mortality rate. (The last consideration is especially significant in view of the fact that the lower mortality rate was obtained in a group of patients who were more severely ill.)

Smaller doses of convalescent serum than have been previously used have been found to be effective.

8. Fox, M. J.: Human Convalescent Serum in the Prevention and Treatment of Scarlet Fever, Wisconsin M. J. **39**:111 (Feb.) 1940.

RECOVERY FROM MULTIPLE RHEUMATOID ARTHRITIS COMPLICATED BY AMYLOIDOSIS IN A CHILD

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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An unusual and dangerous complication of rheumatoid arthritis is visceral amyloidosis. We have had the opportunity to study a child who recovered from severe multiple rheumatoid arthritis (Still's disease) complicated by generalized amyloidosis. Because of the paucity of records of similar cases we believe it important to report this case and to review the related literature.

REPORT OF CASE

R. B., was first admitted to the Mount Sinai Hospital when she was 14 years of age. Her illness dated from November 1935, when, at the age of 11, she entered another hospital complaining of sore throat, vomiting and pain in the joints of one week's duration. Tenderness and stiffness of the joints of the arms and legs were found, but there were no deformities. Therapy included two blood transfusions for mild anemia and removal of hypertrophied diseased tonsils.

In the subsequent two years the patient had numerous exacerbations of severe polyarthritis, requiring three additional hospitalizations. Swelling, limitation of motion and deformities of the proximal phalangeal joints and of the joints at the wrists, elbows and knees developed, accompanied by mild anemia, low grade fever, loss of weight and malaise. Definite improvement occurred during the last hospitalization in 1936, and the patient progressed to what she considered complete recovery during a convalescence at the seashore. She returned to her home in July 1937 and attended school regularly for almost six months.

In February 1938 a febrile illness diagnosed as "la grippe" ushered in a severe recurrence of polyarthritis which subsided after a brief period of rest in bed but recurred with the new symptom of severe precordial pain which was aggravated by respiration. The patient was admitted to the medical ward of Mount Sinai Hospital April 20, 1938.

The patient's complaints at the time of admission were pain, swelling and some limitation of motion of the proximal phalangeal joints and of the joints at the wrists, elbows and knees, nocturnal chills, cold sweats, fever, sore throat, anorexia, malaise, loss of weight, frequent palpation, dull precordial pain and occasional abdominal pain. Menarche had occurred one year previously, and the patient's menstrual periods were irregular with scanty flow. Her past medical history other than that already described and her family history revealed no contributory factors.

At the time of the physical examination the patient's oral temperature was 99.2 F.; her pulse rate was 90 and her blood pressure was 110 at systole and 70 at diastole. There were mild chronic pharyngitis, slight cervical adenopathy, edema, pain and limitation of motion of the proximal phalangeal joints and of the joints at the elbows, knees and ankles. The spleen was barely palpable. Some atrophy of the muscles of the upper and lower extremities due to disuse was noted. The vertebral column was not involved. Aside from tachycardia the action of the heart was normal; the lungs were clear.

The significant laboratory data obtained during our observation of this patient are reported in the accompanying table. The blood contained 10.1 Gm. of hemoglobin per hundred cubic centimeters (70 per cent) and 3,300,000 erythrocytes per cubic millimeter. After she had received three blood transfusions, totaling 990 cc., and ferrous sulfate orally, the hemoglobin content of the blood was elevated to 11.8 Gm. (80 per cent) and the number of erythrocytes to 4,510,000. The erythrocyte sedimentation rate was constantly rapid. Tests of blood for agglutination against brucella antigens showed no antibody present. The reactions to the Wassermann and Kahn tests were negative. Several cultures of blood were sterile. The sugar content, carbon dioxide–combining power, uric acid content and chloride content of the blood were within normal limits. There was no cutaneous reaction to tuberculin. A normal icterus index, normal phosphatase activity of the serum and a normal reaction to the sulfobromophthalein test indicated unimpaired hepatic function. Roentgenograms of the skeleton revealed arthritic changes in the joints, generalized osseous rarefaction with areas suggesting the formation of cysts and mild pulmonary fibrosis; the heart was of normal size, but there was slight dilatation of the pulmonary conus.

The patient received a high vitamin, high caloric diet supplemented with vitamin B complex. Salicylates were poorly tolerated, and toxic symptoms followed a brief trial of intravenous administration of neoarsphenamine. An autogenous vaccine was prepared from material obtained from the nose and throat of the patient, but only two injections were given.

The patient's course in the hospital was one of continuous pain in the joints, relieved only by analgesics and narcotics, low grade fever, loss of weight and

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malaise. An effusion which developed in the right knee joint required aspiration on several occasions. The aspirated fluid was sterile on culture, and inoculation of a guinea pig revealed no evidence of tuberculosis.

In July 1938 puffiness of the face, hypoproteinemia, gross inversion of the albumin-globulin ratio and moderate proteinuria suggested the onset of the nephrotic syndrome due to renal amyloidosis. The patient was given a high protein diet and frequent transfusions of plasma, but the protein content of the blood fell rapidly to a low level. In the light of recent experience it is probable that insufficient quantities of plasma were administered. The cholesterol content of the blood became elevated, and the basal metabolic rate was low. The reactions to several congo red tests were diagnostic of amyloidosis. Concentration tests of renal function showed fixation of specific gravity. Massive proteinuria developed, and the spleen became larger and the liver definitely palpable. Desiccated thyroid was given for several days, but the administration was stopped because improvement was 73.5 per cent of normal. The temperature previously elevated and fluctuating remained level, never rising above 99.2 F.

After two weeks' "vacation" at home in December 1938 the patient returned for further observation because of increasing severity of pain in the joints and recurrence of facial edema. Her face was pale, and there was moderate periorbital edema. The left elbow joint was tender, swollen and deformed, and the proximal phalangeal and metacarpophalangeal joints of both hands revealed the classic deformities of severe rheumatoid arthritis. Mild anemia, leukocytosis, massive proteinuria and severe cylindruria were found. Doubly refractile lipid bodies could not be demonstrated in the urine. Despite adequate thyroid medication the patient's basal metabolic rate was minus 13 per cent and the blood contained 320 mg. of cholesterol per hundred cubic centimeters. Roentgen examination of the bones and joints showed no changes from the conditions reported on the initial admission of the patient.

Laboratory Data for Patient with Rheumatoid Arthritis Complicated by Amyloidosis

Date	Arthritis	Edema	Hepatomegaly	Splenomegaly	Blood: Total Proteins, Gm./100 Cc.	Blood: Albumin, Gm./100 Cc.	Blood: Globulin, Gm./100 Cc.	Proteinuria	Congo Red Retention, %	Erythrocyte Sedimentation Rate, Mm./60 Min.	Blood Calcium, Mg./100 Cc.	Blood Phosphorus, Mg./100 Cc.	Blood Cholesterol, Mg./100 Cc.	Basal Metabolic Rate, %
April 1938	++++	0	0	+	—	—	—	±	—	29	8.8	4.7	140	—
July 2, 1938	++	0	0	+	6.4	1.4	5.0	—	—	27	—	—	—	—
July 19, 1938	++	+	+	++	4.7	1.4	3.3	2.8 Gm. in 24 hr.	70	27	—	—	—	—
July 30, 1938	++	+	+	++	3.5	2.3	++	—	—	—	—	—	—	−18
August 1938	+++	++++	+	++	3.38	0.98	2.4	++++	90	—	—	—	310	—
September 1938	++	+++	+	++	3.0	1.1	1.9	++++	95	33	7.6	5.9	480	−22
October 1938	++	++	+	++	3.8	1.9	1.9	++++	95	—	—	—	460	−19
November 1938	++	+	—	—	3.5	1.8	1.7	++++	90	32	—	—	—	−17
December 1938	+++	0	0	0	3.5	1.1	2.4	++++	90	..	8.5	—	320	−13
January 1939	+++	+	0	0	4.1	1.4	2.7	++++	—	36	7.4	4.9	210	−20
February 1939	++	0	0	0	3.4	1.2	2.2	++++	80	32	8.7	5.3	190	−16
March 1939	++	+	0	0	4.1	1.9	2.2	++++	75	29	—	—	400	−18
April 1939	+	0	0	0	3.5	1.1	2.4	—	85	..	7.3	4.8	304	— 6
May 1939	+	0	0	0	3.6	1.7	1.9	++++	70	29	8.1	5.1	206	−13
June 1939	+	0	0	0	3.8	1.4	2.4	—	65	—	—	—	320	−10
July 1939	+	0	0	0	3.8	1.4	2.4	++++	—	29	7.5	—	360	—
April 1940	—	0	0	0	5.7	3.0	2.7	±	65	24	9.1	4.6	272	+11
June 1943	0	0	0	0	5.7	3.4	2.3	—	15	5	10.7	3.4	178	+ 4

A minus sign indicates that the data are not available; a zero indicates that absence of the symptom indicated was noted.

of the onset of diarrhea and melena which lasted over four weeks. A proctoscopic examination of the rectum during this episode revealed multiple tiny ulcerations of the rectal mucosa. Severe edema, progressing to anasarca with massive pleural effusions and ascites, occurred in August, and the outlook appeared grave. Various xanthine and mercurial diuretics were alternately mildly effectual and ineffectual in producing diuresis. In the face of these developments additional protein was administered in the diet and by means of transfusions of plasma.

Encouraged by the report of Grayzel and Jacobi[1] concerning the value of powdered desiccated whole liver, we gave the patient frequent injections of liver extract for many months.

Gradual slow improvement ensued despite the persistence of the now stationary arthritic manifestations and of hypoproteinemia with relative hyperglobulinemia. By October 1938 the pleural effusions and ascites had disappeared and the peripheral edema had lessened appreciably. Urea clearance during the period of

Because of the development of wrist drop the right wrist was supported in a plaster cast. Buck's extension applied to the left leg relieved severe pain which had developed in the left hip. The patient remained in the hospital for seven months after the second admission and showed slow gradual improvement, with disappearance of edema and pain in the joints, restoration of partial function of all the joints involved, maintenance of normal blood count without transfusions, gain in weight and return of a sense of well-being. The clinical improvement occurred despite persistence of the abnormal blood chemistry and of the low basal metabolic rate. The patient was discharged on July 28, 1939, walking with the aid of canes and the support of metal braces.

Several months in a seashore convalescent home[2] produced a striking improvement. The child returned to our wards in April 1940 because of slight pain in the left elbow joint and mild fatigue. Examination revealed some enlargement and deformity of the proximal phalangeal joints of the right hand, with

1. Grayzel, H. G., and Jacobi, M.: Secondary Amyloidosis, Ann. Int. Med. **12**:39-58 (July) 1938.

2. Bachrach Home for Crippled Children, Atlantic City, service of Dr. A. Rechtman, Philadelphia.

excellent function of the fingers and hands, crepitus and flexion of the right wrist and enlargement of the knee joints. All the joints were painless except the left elbow, which was slightly tender, and all showed full range of motion. There was no edema and no hepatosplenomegaly. The pain in the left elbow subsided quickly, and aside from the residual deformities of the joints the patient appeared to be in excellent health. The results of all laboratory studies were more nearly normal (table). Urine was concentrated to a specific gravity of 1.023; urea clearance was 100 per cent of normal, and there was no anemia.

The patient was last seen in June 1943. She was free of symptoms and was leading an active life. She walked with a scarcely discernible list to the left and exhibited an almost complete disappearance of all deformities of joints, and her liver and spleen were not palpable. All of the laboratory studies now gave results within normal limits.

COMMENT

Amyloidosis is probably a metabolic disease representing a fundamental deviation from normal endogenous protein metabolism resulting in the production and deposition of a foreign protein called amyloid. It may occur without apparent cause [3] but usually follows, or is found in association with, a chronic disease process, such as tuberculosis, syphilis, chronic suppuration, cancer or multiple myeloma. Its occurrence has been attributed to the hyperglobulinemia that sometimes accompanies certain chronic diseases and that follows long-continued vaccine therapy.[4] Davis [5] found absolute and relative hyperglobulinemia in persons with severe infectious arthritis. We cannot attribute the onset of amyloidosis in our patient to the presence of hyperglobulinemia. The globulin content of the serum was always within normal limits, though relatively elevated in comparison to the albumin content. The patient's clinical improvement did not parallel the return of the protein content of the blood to normal. The amount of vaccine administered could not have been an amylogenic factor as in the case reported by Reimann and Eklund.[4] Moschcowitz [6] emphasized the rarity of amyloidosis in nonsuppurative maladies and pointed out that the occasional association of the two conditions did not always infer a cause and effect sequence. In those instances in which amyloidosis complicates infectious arthritis its onset invariably follows that of the arthritis by several years. Recovery from amyloidosis has been reported, however, when the state of the arthritis remained unchanged.[7] Therefore, we can say only that the development of amyloidosis in this instance was probably directly related to the arthritis, but so far as the cause of both pathologic states is unknown any decision as to the cause would be only speculation.

Amyloidosis is usually a progressive fatal disease recovery from which has been called a clinical curiosity.[8] Reports of at least 29 cases of amyloidosis have appeared since 1880.[9]

The diagnosis of regression of amyloidosis prior to the introduction of the congo red test [10] has been questioned,[9q] but in only 4 of the 29

3. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Primary Amyloidosis Limited to Tissue of Mesodermal Origin, Am. J. Path. **11**:977-988 (Nov.) 1935.

4. Reimann, H. A., and Eklund, C. M.: Long-Continued Vaccine Therapy as a Cause of Amyloidosis, Am. J. M. Sc. **190**:88-92 (July) 1935.

5. Davis, J. S., Jr.: Protein Studies in Atrophic (Rheumatoid) and Hypertrophic Arthritis, J. Lab. & Clin. Med. **21**:478-490 (Feb.) 1936.

6. Moschcowitz, E.: Clinical Aspects of Amyloidosis, Ann. Int. Med. **10**:73-78 (July) 1936.

7. Kennedy, W. R.: Renal Amyloidosis, Canad. M. A. J. **33**:385-388 (Oct.) 1935.

8. Rosenblatt, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis: Report of Case, Arch. Int. Med. **57**:562-565 (March) 1936.

9. (*a*) Kretzschmar, P. H., and Westbrook, B. F.: A Case of Chronic Empyema with Extensive Amyloid Degeneration: Recovery, Proc. M. Soc. County Kings **5**:343-348, 1880-1881. (*b*) Owen, I.: Recovery from Advanced Lardaceous Disease, Proc. M. Soc. London **9**:18-19, 1886. (*c*) Gairdner, W. T., in discussion on Delafield, F.: On the Diseases of Kidneys Popularly Called Bright's Disease, Tr. A. Am. Physicians **6**:124-153, 1891. (*d*) Herringham, W. P.: Kidney Diseases, London, Oxford University Press, 1912, p. 353. (*e*) Waldenström, H.: Ueber das Entstehen und Verschwinden des Amyloids beim Menschen, Klin. Wchnschr. **6**:2235-2237 (Nov. 19) 1927. (*f*) Walker, G. F.: A Case of Recovery from Amyloid Disease, Lancet **2**:120 (July 21) 1928. (*g*) Nathan, M.: Ueber die klinische Diagnose der Amyloidose mittels Kongorotinjectionen, München. med. Wchnschr. **75**:1883-1884 (Nov. 2) 1928. (*h*) Métraux, R.: Ueber Rückbildungsvorgänge bei menschlicher Amyloidose, Frankfurt. Ztschr. f. Path. **37**:279-292, 1929. (*i*) Whitbeck, B. H.: Liver Meal in the Treatment of Amyloidosis in Surgical Tuberculosis, J. Bone & Joint Surg. **14**:85-92 (Jan.) 1932. (*j*) Grayzel, H. B.; Jacobi, M.; Warshall, H. B.; Bogin, M., and Bolker, H.: Amyloidosis, Arch. Path. **17**:50-75 (Jan.) 1934. (*k*) Habein, H. C.: Amyloidosis: Report of Case in Which Patient Recovered, Proc. Staff Meet., Mayo Clin. **9**: 261-262 (May 2) 1934. (*l*) Reimann, H. A.: Recovery from Amyloidosis, J. A. M. A. **104**:1070-1071 (March 30) 1935. (*m*) Kennedy.[7] (*n*) Rosenblatt.[8] (*o*) Oppenheimer, B. S., and Silver, S.: Recession of Renal Amyloidosis Due to Multiple Skin Gangrene Associated with Arteritis of Skin, J. Mt. Sinai Hosp. **4**:851-860 (March-April) 1938. (*p*) Grayzel and Jacobi.[1] (*q*) Peariman, A. W.: Regression of Amyloidosis, Quart. Bull., Sea View Hosp. **6**:92-97 (Oct.) 1940.

10. Bennhold, H.: Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **142**:32-46 (March) 1923.

cases[11] is this criticism warranted. In most instances recoveries occurred in patients in whom the primary disease had been eradicated; regression of amyloidosis may occur, however, when the primary disease is still active. Grayzel and Jacobi[9p] reported the disappearance of all clinical signs of amyloidosis in 6 patients with persistent chronic suppurative disease and ascribed the cures to the oral administration of powdered whole liver. In one of Pearlman's cases[9q] of amyloidosis secondary to pulmonary tuberculosis the amyloid disease regressed though the patient had not been completely cured of the tuberculous infection. Our patient still had clinical evidence of active arthritis and her sedimentation rate was rapid when amyloidosis had apparently completely regressed. Regression of the primary disease, therefore, is not a necessary condition for recovery from amyloidosis.

The use of powdered liver extracts in the treatment of amyloidosis is based on the experimental work in amyloidosis by Grayzel, Jacobi and Warshall.[12] They noted resorption of amyloid in animals in the early stages of amyloidosis when powdered whole liver was added to the diet.

The reports of Whitbeck[9l] and of Grayzel and Jacobi[1] concerning the value of powdered extract of liver in the treatment of secondary amyloidosis are encouraging and indicate that the treatment deserves further clinical trials. A careful review of Rosenblatt's case[8] gives us the impression that liver therapy was greatly responsible for the regression of amyloidosis. Although our patient experienced the gamut of polytherapy, improvement became manifest only after we administered large doses of crude liver extract.

REVIEW OF THE LITERATURE

Following the publication of reports by Whitman[13] and Spitzy[14] in 1903 of cases of arthritis complicated by amyloidosis twenty-four years elapsed without a similar report appearing in the literature. Carroll and Nelson[15] revived interest in this unusual syndrome with their report in 1927, and to date reports of 31 cases have been published.[16] Adequate data on all but 4 of these cases[17] are available.

Cases in which arthritic symptoms were probably caused by large amounts of amyloid deposited in joints[18] have been omitted from our analysis.

In the cases for which the sex of the patient was recorded 21 were male and 8 were female. This distribution differs from the ratio of 1 man to 2 women usually reported in large statistical studies of the incidence of uncomplicated chronic arthritis.[19]

The age of the patient was stated in the reports of 29 cases. Six patients were under 10 years, 4 were between 11 and 20 years, 5

11. Kretzschmar and Westbrook.[9a] Owen.[9b] Gairdner.[9c] Herringham.[9d]

12. Grayzel, Jacobi and Warshall, cited by Moschcowitz.[6]

13. Whitman, R.: A Report of Final Results in Two Cases of Polyarthritis in Children of the Type First Described by Still, Together with Remarks on Rheumatoid Arthritis, M. Rec. **63**:601-606 (April 18) 1903.

14. Spitzy, H.: Zur chronischen Arthritis des Kindes, Ztschr. f. orthop. Chir. **11**:699-795, 1903.

15. Carroll, J. H., and Nelson, R. L.: Still's Disease with Amyloidosis, Arch. Pediat. **44**:187-190 (March) 1927.

16. (*a*) Whitman.[13] (*b*) Spitzy.[14] (*c*) Carroll and Nelson.[15] (*d*) Zadek, E.: Ueber Urämie bei Amyloidniere, Klin. Wchnschr. **8**:249-252 (Feb. 5) 1929. (*e*) Volhard, R., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, vol. 6, pt. 2, p. 1050. (*f*) Hardgrove, M. A. F.: Retention of Congo Red in Amyloid Disease, Arch. Path. **15**:238-243 (Feb.) 1933. (*g*) Bell, E. T.: Amyloid Disease of the Kidneys, Am. J. Path. **9**:185-204 (March) 1933. (*h*) Amyloid Disease of Kidneys, Spleen and Liver, Cabot Case 1942, New England J. Med. **208**:757-759 (April 6) 1933. (*i*) Rosenblatt, M. B.: Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **186**:558-567 (Oct.) 1933. (*j*) Dixon, H. M.: Renal Amyloidosis in Relation to Renal Insufficiency, ibid. **187**:401-411 (March) 1934. (*k*) Perla, D., and Gross, H.: Atypical Amyloid Disease, Am. J. Path. **11**:93-112 (Jan.) 1935. (*l*) Reimann and Eklund.[4] (*m*) Kennedy.[7] (*n*) Moschcowitz.[6] (*o*) Colver, T.: The Prognosis in Rheumatoid Arthritis in Childhood, Arch. Dis. Childhood **12**:253-260 (Aug.) 1937. (*p*) Oppenheimer and Silver.[9o] (*q*) Portis, R. B.: Pathology of Chronic Arthritis of Children (Still's Disease), Am. J. Dis. Child. **55**:1000-1017 (May) 1938. (*r*) Schneiderbauer, A.: Nephrose bei chronischer Polyarthritis, Ztschr. f. klin. Med. **133**:643-647, 1938. (*s*) Still's Disease, Cabot Case 24372, New England J. Med. **219**:394-398 (Sept. 15) 1938. (*t*) Imrie, A. H., and Aitkenhead, A. C.: Amyloidosis Complicating Still's Disease, Lancet **2**:421-422 (Aug. 19) 1939. (*u*) Oxer, G. M.: Amyloidosis Complicating Rheumatoid Arthritis, M. J. Australia **1**:233-234 (Feb. 17) 1940. (*v*) Gordin, R.: Amyloidosis in Chronic Nonsuppurative Diseases of Joints, Nord. med. (Finska läk.-sällsk. handl.) **11**:2609-2612 (Sept. 13) 1941. (*w*) Villaret, M.; Justin-Besancon, L., and Rubens-Duval, A.: Rheumatismes chroniques et amylose, Presse méd. **49**:987-989 (Sept. 17-20) 1941. (*x*) Baggenstoss, A. H., and Rosenberg, E. F.: Visceral Lesions Associated with Chronic Infectious (Rheumatoid) Arthritis, Arch. Path. **35**:503-516 (April) 1943. (*y*) Solomon, W. M.: Amyloidosis in Chronic Atrophic Arthritis, Ann. Int. Med. **18**:846-850 (May) 1943.

17. Portis.[16q] Rosenblatt.[16i] Gordin.[16v]

18. (*a*) Feller, F.: Amyloidose der Gelenke, Centralbl. f. allg. Path u. path. Anat. **63**:123 (July 30) 1935. (*b*) Lengh, F.: Zur Kenntnis der Amyloidablagerung in den Gelenken, ibid. **69**:1-5 (Dec. 10) 1937. (*c*) Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis, Arch. Path. **27**:267-288 (Feb.) 1939.

19. Pemberton, R., and Peirce, E. G.: Clinical and Statistical Study of Chronic Arthritis Based on 1,100 Cases, Am. J. M. Sc. **173**:31-46 (Jan.) 1927.

were between 21 and 30 years, 2 were between 31 and 40 years, 7 were between 41 and 50 years, 2 were between 51 and 60 years and 3 were between 61 and 70 years. The age of the patient was not stated in the reports of 2 cases. Nine cases have been reported in which the patient was less than 16 years of age.

In 28 cases arthritis preceded the onset of amyloidosis. The shortest interval between the onsets of the two conditions was one and one-half years, the longest sixteen years and the average for the series six and a half years.

In 17 cases arthritis was severe and in 7 cases moderately severe. To our knowledge amyloidosis has never appeared with mild infectious arthritis.

In many cases severe loss of weight, wasting and cachexia were noted. Low grade fever was frequent. Bouts of diarrhea, such as our patient experienced, were commonly mentioned complications.

Hepatomegaly, splenomegaly and edema are important clinical signs of amyloidosis, but their presence is not essential to the diagnosis,[20] because unequal involvement of the viscera obtains in some cases. In Rosenblatt's series of 125 cases of amyloidosis unrelated to arthritis,[161] only the spleen and kidney were ever involved alone—the spleen 12 times and the kidney twice. When the nephrotic syndrome with edema predominates, renal involvement is extensive and the liver and spleen may contain only small focal deposits of amyloid and show little or no enlargement. Of 20 patients with amyloidosis complicating rheumatoid arthritis, 4 showed hepatomegaly alone, 1 showed splenomegaly alone, 8 showed hepatosplenomegaly and 7 showed neither hepatomegaly nor splenomegaly. In 27 reports of cases in which mention of the presence or absence of edema was made, generalized anasarca was reported for 5 patients, moderate edema for 8 and absence of edema for 11. These 11 patients without edema made up the majority of those showing hepatosplenomegaly or hepatomegaly alone. Ascites and signs of collateral circulation were not seen in any patient with amyloid hepatomegaly.

The blood pressures of patients with arthritis complicated by amyloidosis, even when the nephrotic syndrome due to renal involvement was present, were usually within normal limits; Rosenblatt[161] found no patient with systolic blood pressure exceeding 140 mm. of mercury and only 3 with pressures exceeding 130 mm. in 125 patients with amyloidosis. Tuberculosis, which was the primary disease in the majority of his 110 patients, characteristically caused hypotension. He commented that "in cases of amyloidosis in which the underlying disease is not as chronic as pulmonary tuberculosis, amyloid involvement of the kidney has occasionally been found associated with hypertension." Of 14 persons with arthritis complicated by amyloidosis, 1 was reported as having no hypertension; 8 had systolic blood pressures of between 101 and 120 mm., 3 had pressures of between 121 and 149 mm. and 2 had pressures of 150 mm. or higher. The blood pressure was not stated in the reports of 17 patients. Two of 14 patients showed systolic hypertension if we accept 150 mm. systolic as the upper limit of normal.

Anemia was present in 12 of 18 patients. Four of these patients had less than 3,000,000 red cells per cubic millimeter of blood; the remaining 8 had between 3,000,000 and 4,000,000. Leukocytosis was noted in 7 of 14 patients. Five of these had 10,000 to 20,000 white cells per cubic millimeter, and 12 had over 20,000.

The appearance of albuminuria has been suggested as the important sign heralding the clinical onset of renal amyloidosis.[21] Rosenblatt[161] examined the urine of 109 persons with amyloidosis and found albuminuria in 77. Of these 65 showed amyloid involvement of the kidney, and Rosenblatt was able to find other conditions to account for the albuminuria in 8 of the remaining 12. Saleeby[22] noted albuminuria in 29 of 40 patients with renal amyloidosis. In our review of the literature of 23 cases of arthritis with amyloidosis, we found that albuminuria was reported as absent in only 2; it was reported as severe in 12 and moderate in 9 cases.

Hypoproteinemia is common in persons with renal amyloidosis and is mainly responsible for the production of edema. There is no direct relationship between the extent of albuminuria and the production of edema.[161] However, dysfunction of the liver, which has been reported as present in patients with severe rheumatoid arthritis,[23] may contribute to the reduction of the blood proteins. Of the reports of 5 cases of amyloidosis with arthritis in which the blood pro-

20. Mark, M. F., and Mosenthal, H. O.: Kidney Function and Uremia in Renal Amyloidosis, Am. J. M. Sc. **196**:529-539 (Oct.) 1938.

21. Pearlman, A. W.: Amyloidosis: Clinical and Pathological Study of One Hundred and Thirty-Five Cases, Quart. Bull., Sea View Hosp. **6**:295-308 (April) 1941.

22. Saleeby, E. R.: Question of Existence of Amyloid Casts, J. A. M. A. **84**:344-345 (Jan. 31) 1925.

23. Rawls, W. B.; Weiss, S., and Collins, V. L.: Liver Function in Rheumatoid (Chronic Infectious) Arthritis: Preliminary Report, Ann. Int. Med. **10**: 1021-1027 (Jan.) 1937.

tein was studied only 1 [16h] gave values as low as were obtained in our patient; the albumin-globulin fractions were not reported by these authors. In 2 cases the values for total protein were normal, but in 1 of these the albumin-globulin ratio was reversed. In 2 cases values for total protein of between 4 and 5 Gm. per hundred cubic centimeters of blood with reversal of the albumin-globulin ratio were reported.

The retention of intravenously administered congo red by persons with amyloidosis, first described by Bennhold,[10] is thought to be the most important diagnostic criterion of the disease. Bennhold stated that normally 20 per cent of the congo red disappeared in the first hour, that retention of 40 to 60 per cent occurred only in nephrosis or amyloidosis and that retention of 60 per cent or greater was diagnostic of amyloid disease. Lipstein [24] correlated the percentage of dye absorbed clinically with the presence or absence of amyloid at autopsy and concluded that the results were diagnostic for amyloidosis only when 90 per cent or more of the injected dye was retained. However, definitely proved amyloidosis in persons with a retention of only 40 to 39 per cent of the dye has been reported.[25] Congo red tests were reported in 11 cases in this series. In only 1 case was the result reported as negative. In 2 cases the result was reported as positive. Five patients retained from 50 to 90 per cent of the dye, and 3 retained 90 to 100 per cent.

Determinations of blood cholesterol were reported in 5 cases. Of 3 patients with the nephrotic syndrome, 2 had over 205 mg. of cholesterol per hundred cubic centimeters of blood and the third had 175 mg. The remaining 2 patients, with deposition of amyloid primarily in the liver and spleen, had normal values for blood cholesterol.

Seven of 12 patients showed substantial hyperazotemia (blood urea nitrogen, 50 mg. or more per hundred cubic centimeters). Four of these died of uremia and 1 of cardiac failure. The cause of death of the remaining 2 patients was not stated.

The basal metabolic rate, reported for only 1 patient, was minus 25 per cent. The patient presented the nephrotic syndrome.[16f] The blood calcium was of normal amount in the 2 patients for whom it was measured.

Ophthalmic complications were reported in the histories of 5 patients. In 3 the diagnosis was iritis and in 2 iridocyclitis. Oxer [16u] commented on the ophthalmic complications which occurred in both of his patients with arthritis with amyloidosis and noted that 2 other patients with uncomplicated arthritis had similar infections of the eyes, which suggests that the association of iritis with amyloidosis is probably of no significance.

All but 5 of 31 patients with chronic arthritis complicated by amyloidosis are known to have died. Moschcowitz [6] lost track of 2 of the other 5 patients while they still presented the clinical picture of amyloidosis and has not been able to obtain any follow-up to ascertain their ultimate fate.[26] One of Gordin's patients [16v] was discharged improved, but in this instance also there was no follow-up. In the case reported by Oppenheimer and Silver [9o] the condition was complicated by extensive cutaneous gangrene with long-standing suppuration, to which the authors attributed the development of amyloidosis. With regression of the cutaneous lesions the amyloidosis was cured. We believe that Kennedy's patient [7] is the only one aside from ours that can be considered as having recovered from amyloidosis following chronic infectious (rheumatoid) arthritis. The true mortality rate, therefore, of this combination of pathologic entities based on the cases reported in the literature with 4 cases excluded for the reasons mentioned and with our own case added, is 93 per cent. The cause of death was uremia in 7 cases, bronchopneumonia and uremia in 2, septicemia and lateral sinus thrombosis in 1, cardiac failure in 1, abdominal hemorrhage in 1 and severe erysipelas in 1. The cause was not stated in the reports of 13 cases.

At autopsy amyloid involvement was found to be primarily renal in 8 cases, splenic in 1, hepatic in 2, hepatic and splenic in 4 and splenic and renal in 2. The degree of amyloid involvement of the various viscera was not stated in the reports of 9 cases.

It was difficult in reviewing the protocols of these cases to correlate the postmortem observations with the clinical pictures, but in general severe amyloid involvement of the kidneys produced renal failure and death from uremia, whereas involvement of the liver and spleen primarily was not associated with renal failure. The adrenal glands were involved in 7 cases, but in no instance was adrenal failure produced. In 1 case the capillaries of the thyroid and submaxillary glands,[16t] in another the thyroid

24. Lipstein, S.: Evaluation of Congo Red Test: Correlation of Autopsy Findings and Dye Absorption in One Hundred and Twenty-Five Cases, Am. J. M. Sc. **195**:205-211 (Feb.) 1938.

25. Altnow, H. O.; Van Winkle, C. C.; Maly, H. W., and Williams, L. E.: Renal Amyloidosis: Clinical Course and Pathologic Lesions in Sixteen Cases, Arch. Int. Med. **56**:944-975 (Nov.) 1935.

26. Moschcowitz, E.: Personal communication to the author.

capsule [16q] and in 2 cases [27] lymph nodes contained some amyloid.

The presence of amyloid in the spleen, liver, kidneys, esophagus, small intestine, bladder, lymph nodes and thymus was reported in another case.[16x] Pericardial adhesions, often extensive, were found in 8 cases. The presence of transient pericarditis may explain the severe precordial pain suffered by our patient for several weeks.

SUMMARY

From a survey of the literature it is apparent that the development of amyloidosis in the course of rheumatoid arthritis is an unusual occurrence which immediately converts an ordinarily benign disease into one with a high mortality. Amyloidosis never follows mild rheumatoid arthritis but is always preceded by severe or moderately severe arthritis of some duration.

A patient with multiple rheumatoid arthritis (Still's disease) complicated by amyloidosis treated with liver extract recovered. The evidence presented in other reports as well as in the case reported concerning the therapeutic efficacy of liver extract in amyloidosis warrants further clinical trial of this treatment.

27. Whitman.[13] Baggenstoss and Rosenberg.[16z]

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ACTINOMYCOSIS OF THE HEART SIMULATING RHEUMATIC FEVER

REPORT OF THREE CASES OF CARDIAC ACTINOMYCOSIS, WITH A REVIEW OF THE LITERATURE

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Actinomycosis is the most common visceral mycotic infection in man. As early as 1899, ten years after the first description of the disease in man by Israel, Ruhräh [1] presented statistics on 1,094 cases. In 1925 Sanford and Voelker [2] were able to collect reports of 670 cases in the United States alone. In about 15 per cent of these cases the infection occurred in the thorax. This figure has been corroborated by other observers, but, as pointed out by Kaufmann,[3] involvement of the heart and pericardium is distinctly rare. Kasper and Pinner [4] found it to occur in less than 2 per cent of 470 cases of actinomycosis. In his recent excellent monograph on actinomycosis Cope [5] made only one general statement concerning cardiac actinomycosis, namely, "extension by continuity may take the fungus into the pericardium or the very substance of the heart." The following case is an example of this unusual condition in which the clinical symptoms closely simulated those of rheumatic heart disease.

REPORT OF A CASE

N. C., a 30 year old Greek man, was admitted to Montefiore Hospital on Dec. 17, 1935, complaining of cough, dyspnea and weakness of seven and a half months' duration. Five years previously he had been employed as a porter in a concern which handled products made of gelatin. There was nothing significant in the family history. The patient presented no history of any of the manifestations of the rheumatic state or of other possible etiologic factors related to his illness. He had been perfectly well until May 1, 1935, when while walking he had a sudden attack of shortness of breath associated with severe jabbing pain in the precordial region. As a result he was bedridden for the next two months, during which time the precordial pain gradually diminished but the dyspnea persisted and a severe, nonproductive cough developed. When, in July 1935, he attempted to carry on a normal daily routine he found himself weak and readily fatigued and he experienced pain in both scapular regions, especially the right. Because of these complaints he remained bedridden most of the time, and in October 1935 he was admitted to the Norwegian Hospital. There he was found to have systolic and late diastolic murmurs, enlargement of the liver and a small pleural effusion on the right side. Fever and slight leukocytosis were noted. Hemoptysis occurred on two occasions, and at one time a pericardial friction rub was heard. A diagnosis of rheumatic heart disease was made, although the possibility of tuberculous pericarditis was entertained.

When the patient was admitted to Montefiore Hospital, in December 1935, examination revealed a temperature of 100.4 F., a pulse rate of 110 and a blood pressure of 110 systolic and 80 diastolic. The head and neck showed no abnormalities, except slight cyanosis of the lips. By percussion, the heart seemed to be enlarged to the left. The rhythm was regular and the rate somewhat rapid. Blowing systolic and rumbling presystolic murmurs were heard at the apical area. There was no friction rub. At the base of the right lung there was dulness to percussion, with diminished respiratory sounds, suggesting the presence of a small amount of fluid in the pleural cavity. The liver, which was enlarged to the level of the umbilicus, was firm and not tender. The spleen was not felt at that time, but subsequently the tip was palpated just below the left costal margin on several occasions. There was a small amount of edema over the sacrum, but none elsewhere.

The laboratory data were as follows: hemoglobin, 10.5 Gm. per hundred cubic centimeters; red cells, 5,200,000 per cubic millimeter of blood; leukocytes, 15,400 per cubic millimeter, with 84 per cent of them polymorphonuclear; Wassermann and Kahn reactions, negative; erythrocyte sedimentation rate, 26 mm. in one hour; blood urea nitrogen, 7 mg. per hundred cubic centimeters; icterus index, 18 units and venous pressure, 20 cm. of blood. The urinary reaction for albumin was 2 plus and the urine contained few hyaline casts, no red blood cells and only a trace of bile. Roentgen examination of the chest revealed a small amount of fluid at the base of the right lung and some enlargement of the heart in the region of the pulmonary conus.

The patient's course in the hospital was marked by a temperature ranging between 99 and 101 F., despite the administration of moderate doses of acetylsalicylic acid. He complained from time to time of pain in the right scapular area on breathing, but his most distressing symptom was a hacking, virtually nonproductive cough. There was some dyspnea, even at rest,

* Aided by a grant from the Sigmund M. Lehman Fellowship Fund.

From the Laboratory Division and the Medical Division of the Montefiore Hospital for Chronic Diseases.

1. Ruhräh, J.: Actinomycosis in Man with Special Reference to the Cases Which Have Been Observed in America, Ann. Surg. **30**:417, 1899.

2. Sanford, A. H., and Voelker, M.: Actinomycosis in the United States, Arch. Surg. **11**:809 (Dec.) 1925.

3. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, p. 638.

4. Kasper, J. A., and Pinner, M.: Actinomycosis of the Heart, Arch. Path. **10**:687 (Nov.) 1930.

5. Cope, Z.: Actinomycosis, London, Oxford University Press, 1938, p. 146.

and cyanosis was persistent. Treatment with diuretics caused temporary diminution in the edema and decrease in the size of the liver, but later the edema reappeared and the liver again became larger.

On Jan. 27, 1936, six weeks after the patient was admitted to Montefiore Hospital, there was a sudden rise in temperature to 103 F., accompanied with pain in the right posterior portion of the chest. The cough became more severe and productive of rusty sputum. The following day there were signs of consolidation over the middle and lower lobes of the right lung, and on January 29 physical signs and roentgen examination suggested a pleural effusion on the right side. The chest was tapped, and 1,100 cc. of dirty yellow fluid was withdrawn. Bacteriologic study demonstrated Streptococcus haemolyticus. The number of white cells contained 1,100 cc. of turbid, greenish yellow fluid, with fibrin similar to that in the abdomen. The pleura was covered with similar yellowish white fibrinous exudate which could be scraped off easily. The right lung was readily separated from the chest wall. The left pleural cavity contained no fluid. There were a few old fibrous adhesions at the apex of the left lung.

The heart (fig. 2) was left in situ, with the lungs, for purposes of demonstration, and the weights and measurements were not recorded. There were extensive mediastinopericardial adhesions, mostly on the right. The pericardial sac was completely obliterated by dense adhesions throughout. Some silvery scar tissue was present under the endocardium of the left ventricle, below the aortic valve. There was extreme thickening of the right and left auricular walls caused

Fig. 1.—Electrocardiogram for N. C., showing deviation of the axis to the right, sinus tachycardia, notching of the P waves in leads I, II and III, slurring and notching of the ventricular complexes and inversion of T waves in leads II and III. The PR interval is 0.16 second; the QRS interval is widened to 0.12 second. Lead IV (old type) shows notching and slurring of the ventricular complex. Interpretation: disturbance of the system of intraventricular conduction.

in the blood rose from 16,000 to 20,000 per cubic millimeter. Increasing cyanosis and abdominal distention occurred, and the patient died on January 30. A blood culture made two days previously showed hemolytic streptococci.

The clinical diagnosis was rheumatic heart disease, mitral stenosis and mitral insufficiency, with death due to hemolytic streptococcus septicemia with empyema. The primary diagnosis was made on the basis of evidence of congestive heart failure, with murmurs characteristic of mitral disease, leukocytosis, fever, elevated erythrocyte sedimentation rate and electrocardiographic changes consistent with the diagnosis of rheumatic heart disease (fig. 1).

An autopsy was performed seven hours post mortem. There was extreme cyanosis of the lips, ears and finger nail beds. The peritoneal cavity contained 300 cc. of turbid, deep yellow fluid with a large amount of yellowish white fibrin, in clots. The right pleural cavity by the presence of a large amount of firm, pinkish and golden yellow tissue, which appeared to be partly necrotic. The tissue had invaded the epicardium, partly replacing epicardial fat as well as myocardium. Similar areas were present in the right ventricular wall and to some extent in the left ventricular wall (fig. 3). There was no appreciable dilatation of any of the chambers, nor was there any myocardial hypertrophy. The valves and the coronary arteries were entirely normal. The posterior mediastinum, exposed when the esophagus was dissected away, showed evidence of the presence of an inflammatory process productive of scar tissue and pinkish yellow tissue similar to that in the heart and pericardium. This process seemed to have been continuous with a similar condition which involved the greatly thickened diaphragm and the pleura covering the lower lobe of the right lung. The aorta showed no significant changes.

In the right lung the interlobar fissures were obliterated, and there was light greenish yellow fibrin over the upper half of the lung. A purulent effusion was found in the horizontal and oblique fissures. The lower lobe was firm and atelectatic, with areas of broken-down pinkish yellow tissue, some of which contained frank greenish pus. In the space between the diaphragm and the lower lobe of the right lung there were some golden yellow areas of organized exudate, which also involved the lobe in places. There was evidence of pneumonic consolidation in the upper lobe of the right lung, and the middle lobe was firm and congested. The left lung was atelectatic and showed no gross inflammatory changes.

Fig. 2.—Heart of N. C. (case 1), showing massive infiltration of the walls of the right auricle and ventricle by actinomycotic granulation tissue. The pericardial sac is obliterated.

The liver weighed 2,150 Gm. It was enlarged and exceedingly firm and showed evidence of chronic passive congestion. The spleen weighed 320 Gm. and likewise showed chronic passive congestion.

The esophagus contained a small diverticulum, about 6 mm. in diameter, just above the cardia. The diverticulum communicated with the tissue of the posterior mediastinum and was embedded in pinkish yellow scar tissue, similar to that in the mediastinum itself.

Microscopic examination showed that large portions of the myocardium were replaced by inflammatory areas containing numerous lymphocytes, plasma cells and polymorphonuclear leukocytes and some red cells, eosinophils and lipid-laden phagocytes. Many of these sites were necrotic, and several contained centrally situated, typically lobulated actinomycotic masses, with mycelial threads and peripheral clubs. The zone immediately surrounding the fungus consisted chiefly of polymorphonuclear leukocytes. Beyond these abscesses there were fibrosis and hyalinization. There was definite subendocardial fibrosis in the region of the conducting fibers of both the right and the left ventricle. The pericardium, the lower portion of the lower lobe of the right lung and the right side of the diaphragm showed similar fungi and granulation tissue.

A section through the esophageal diverticulum showed the lumen to be filled with a large amount of necrotic material and fibrin, with many enmeshed lymphocytes and some phagocytes. Typical actinomycotic masses were present (figs. 4 and 5). Near the base of the diverticulum the lining epithelium was replaced by necrotic and inflammatory tissue similar to that in the lumen. The esophageal musculature was infiltrated with many lymphocytic collections.

COMMENT

This, then, is a case in which an actinomycotic infection originating in a diverticulum of the

esophagus extended to the adjacent mediastinal tissue, the pericardium and myocardium and the lower portion of the right lung, together with the adjacent pleura and diaphragm. It is of extreme interest not only because it represents an unusual pathologic picture but because the clinical course so closely simulated that of rheumatic fever in almost every finding (including the presence of the presystolic murmur characteristic of mitral stenosis, heard by several observers at two different institutions over a period of several months).

The pathologic picture was also somewhat unusual in that fistulas to the exterior were not present (compare the condition described in the reports of 2 other cases which follow). In thoracic actinomycosis perforation of the wall of the chest takes place in more than 80 per cent of the patients.[6] These fistulas constitute a valuable aid in diagnosis, first, because of their very presence and, second, because of the possibility of discovering the organism in the discharge.

The unusual nature of this case prompted further investigation of the character of cardiac involvement in actinomycosis. Of 6 persons with actinomycotic infection on whom autopsies were performed between 1915 and 1939 at Montefiore Hospital, 2 more were found to have cardiac involvement. The conditions in these 2 patients, with that of the 1 already described, demonstrate the great variability of the clinical picture when the heart is involved in actinomycosis.

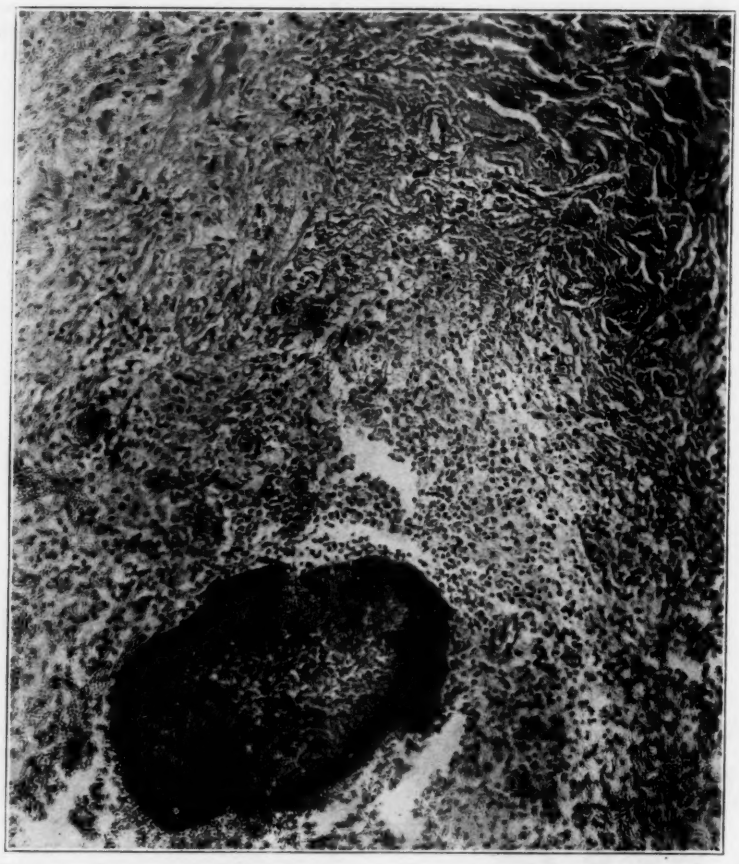

Fig. 3.—Section from a ventricular wall showing a typical actinomycotic mass, with surrounding zone of inflammation, embedded in necrotic cardiac muscle.

REPORTS OF ADDITIONAL CASES

CASE 2.—J. R., an 11 year old boy, was admitted to the hospital March 21, 1917. One year previously he had had pneumonia from which he recovered completely. Six months before admission he began to complain of sharp, constant pain in the left side of the chest, anteriorly, and a persistent cough, productive of yellow sputum. One month later a fluctuating tumor appeared in the left axilla. On incision this was found

6. Ashford, B. K., in Nelson's Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1928, vol. 2, p. 360.

to be an abscess, and the diagnosis of actinomycosis was established.

On examination the patient appeared undernourished and poorly developed. Expansion of the left side of the chest was limited. There was dulness to percussion over the entire left side of the chest and tenderness anteriorly. Respiratory sounds were diminished at the bases of both lungs, and there was bronchial breathing over the left upper part of the chest and amphoric breathing in the axilla. A few fine rales were heard in the left supraclavicular area. Roentgenographic examination showed an extensive, dense shadow occupying all but the base of the left lung field.

fibrosis and several abscess cavities, the contents of which showed sulfur granules. Throughout both lungs were numerous small actinomycotic abscesses, some of which were visible on the surface of the lungs.

The pericardium was completely adherent, except for one area over the right auricle, where it was filled with greenish-yellow, thick, viscid fluid. For demonstration purposes the heart was not dissected free, nor was the cavity opened. Several abscesses were noted in the superficial part of the cardiac muscle when a portion of the pericardium was stripped away. Both kidneys were found to the left of the midline (congenital anomaly) and showed moderate amyloidosis.

Fig. 4.—Section through the esophageal diverticulum of N. C. (Low power). The lumen of the diverticulum is filled with necrotic material in which there appears, as an irregular black area, a typical actinomycotic mass.

During the time the patient was in the hospital, another collection of pus developed in the left scapular area, and later still another, in the left supraclavicular area. Both were incised, and ray fungi were demonstrated in the discharge and in granulation tissue from the walls of the abscesses. As the infection progressed there were spiking fever, severe pain in the chest and profuse expectoration, with the sputum sometimes tinged with blood. The liver became enlarged, eventually to an extreme degree, and at the same time increasing albuminuria was noted. During the latter part of the illness severe dyspnea was present. The patient died on Aug. 6, 1918, apparently as a result of toxemia.

Postmortem examination showed that the left pleural cavity was obliterated completely and the right pleural cavity obliterated almost completely, by adhesions. In the upper lobe of the left lung there were extensive The upper kidney contained a single abscess. There was amyloidosis of the liver and spleen as well as of the kidneys.

Case 3.—A. T. was a 7 year old boy whose illness began in February 1926 with fever and vomiting. Two months later he contracted measles, during which illness he was febrile and lost weight progressively. Because of the progression of these symptoms, he was admitted to the hospital on June 5, 1926. Examination disclosed pallor, signs of fluid at the base of the right lung, a large liver and clubbing of the fingers and toes. A diagnosis of encapsulated empyema was made.

Examination of the blood revealed secondary anemia. The white cells numbered 10,000 per cubic millimeter, with 72 per cent polymorphonuclear leukocytes. The urine was normal. An electrocardiogram showed only deviation of the axis to the left. Roentgen examination

of the chest showed a small pleural effusion on the right side and evidence of consolidation in the upper lobe of the right lung. The heart was enlarged to a moderate degree, both to the right and to the left.

Several attempts to obtain pleural fluid at the time of admission of the patient were unsuccessful, but one month later a swelling appeared at the site of the punctures. Roentgen examination at this time showed disappearance of the pleural effusion, with residual pulmonary infiltration. Six and one-half weeks after the patient was admitted to the hospital the swelling was incised. The pus obtained was sterile on culture, but a specimen of tissue removed from the wall of the chest showed actinomycosis. The patient failed to improve, despite large doses of iodine, transfusion and a second incision of the affected areas. Three months later the pleural effusion recurred and the presence of ascites was determined. Examination of the ascitic fluid revealed that it was a transudate. Distinct enlargement of the heart was noted at this time. A nonproductive cough, an increasing febrile reaction, leukocytosis and progressive anemia developed. The patient died on Sept. 20, 1926.

Postmortem examination revealed an area of thin, purplish skin over the lower part of the right side of the chest, posteriorly. In this area were several sinuses from which a small amount of creamy yellow pus exuded. Incision into this area revealed a mass of necrotic tissue containing numerous areas of fibrosis and small foci of liquefaction. From this area several sinuses ran through the muscles of the back and downward along the vertebral column as far as the sacrum. The necrotic mass was found to involve the lower part of the right lung, the diaphragm and the right kidney.

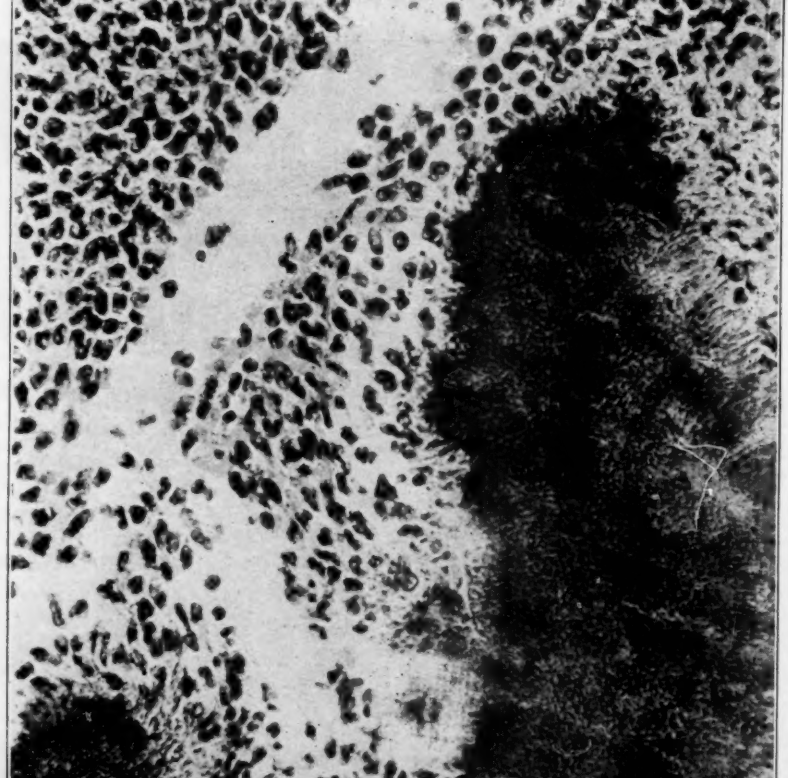

Fig. 5.—Typical mass of actinomycotic ray fungus (high power).

The posterior and inferior part of the right pleural cavity was obliterated by this mass of necrotic tissue. The remainder of the pleural surface showed fibrinous deposits and adhesions, and there were dense pleuropericardial adhesions. On section, most of the lower lobe of the right lurg showed consolidation and num-

erous firm, yellow necrotic areas. The middle lobe contained one nodule of pink tissue with small yellow foci, and the upper lobe was congested and edematous. On the left side, the pleura showed a fibrinopurulent deposit and the lung was atelectatic.

The bronchi contained mucopurulent material. The glands at the bifurcation of the trachea were greatly enlarged and pinkish, but without necrotic areas. In the posterior mediastinum was a mass of necrotic tissue continuous with that on the posterior surface of the right lung and extending up to the enlarged glands. On section, the glands showed only atrophy of the lymphoid tissue and hyaline change.

The pericardial sac was completely obliterated by dense adhesions, in which there were small collections of pus. At its lower right posterior angle the pericardium was replaced by necrotic tissue, continuous with that in the lower lobe of the right lung and the mediastinum and extending into the wall of the right auricle, narrowing the inferior vena cava at the point of entrance and pushing up the endocardium at this point into two small, yellowish white polypoid excrescences. The entire thickness of the wall, with the exception of the endocardium, was replaced by necrotic tissue. There was moderate dilatation of the right auricle and ventricle and a slight degree of hypertrophy of the right ventricle. The left auricle was slightly dilated and hypertrophied and the left ventricle slightly hypertrophied. The valves were normal. The heart weighed 250 Gm.

The lower third of the esophagus was embedded in necrotic tissue, which invaded the muscle but not the mucous membrane. The peritoneal cavity contained no fluid or adhesions. The left kidney had a single small area of necrotic tissue, about 5 mm. in diameter, at the junction of the cortex and the medulla. The right kidney showed invasion at the upper pole by the mass of necrotic tissue coming through the diaphragm. The liver was large and firm but was not invaded by the adjacent necrotic tissue. The spleen was greatly enlarged (200 Gm.) and showed extreme amyloidosis.

In these 2 cases, as opposed to the first case, no difficulty was encountered in establishing the diagnosis of the primary disease, actinomycosis, and in both instances postmortem examinations revealed that the infection had extended from the lung to involve the pericardium and a portion of the myocardium. In the second case the patient (J. R.) had no signs or symptoms of cardiac involvement, whereas in the patient described in case 3 (A. T). the enlargement of the heart and of the liver, the ascites and possibly the dyspnea resulted from the extensive involvement of the pericardium with constriction of the inferior vena cava.

REVIEW OF THE LITERATURE

Sixty-eight cases[7] of actinomycosis with cardiac involvement have been reported in the literature. The largest group of such cases previously reviewed was that of Kasper and Pinner.[4] It included 20 cases. Earlier reviews of the subject were written by Letulle and Hufnagel[8] (1919) and by Thévenot[9] (1903). It should be pointed out that the latter included several cases which when traced back proved not to be cases of genuine cardiac actinomycosis and which therefore do not appear in our tables.

On the basis of pathogenesis, the 68 cases have been classified into five groups and tabulated as follows: table 1, involvement of the heart by direct extension, 29 cases; table 2, involvement of the heart from a distant focus (pyemic), 19 cases; table 3, mode of involvement of the heart not clear, 5 cases; table 4, pericardial lesion not definitely shown to be actinomycotic but evidently the result of the extension of a contiguous actinomycotic lesion from a neighboring viscus (reactive pericarditis), 12 cases; table 5, reported actinomycosis of the heart for which the evidence was so inadequate that the validity of the diagnosis was questionable, 3 cases.

It should be pointed out that in 2 of the cases listed in table 1 the patients had secondary, pyemic involvement of the heart in addition to primary involvement by direct extension (cases of Werthemann and Paetzold).

INCIDENCE OF CARDIAC ACTINOMYCOSIS

Age.—Of the cases listed in tables 1, 2 and 3 there are 48 in which the age of the patient could be ascertained. Thirty-six of the patients were in the second, third and fourth decades of life. A complete tabulation of the incidence in relation to age is as follows:

Type of Cardiac Involvement	Decade					
	First	Second	Third	Fourth	Fifth	Sixth
By direct extension	1	6	4	9	4	1
Pyemic	1	2	6	6	2	1
Uncertain	..	1	1	1	1	1
Reactive	..	1	1	3	5	2

The distribution in relation to age shows no significant variation from that characteristic of actinomycosis in general.

Sex.—Of the cases listed in the first four tables, the sex of the patient was known in 60. Forty-nine of the patients were men and boys. Predilection for males is a well recognized characteristic of actinomycosis in general. It is perhaps

7. Not included was a case cited by Paetzold as appearing in Lenhartz' book "Mikroskopie am Krankenbett" (Lenhartz, H.: Mikroskopie und Chemie am Krankenbett, ed. 6, Berlin, Julius Springer, 1910) as one of actinomycosis breaking into the cavities of the heart. The edition mentioned (1910) was not available. The 1907 and 1922 editions describe no such case, but the latter contains a report of a case of actinomycosis without cardiac involvement (Lenhartz, H.: Mikroskopie und Chemie am Krankenbett, ed. 10, Berlin, Julius Springer, 1922).

8. Letulle, M., and Hufnagel, L.: L'actinomycose du coeur, Bull. Acad. de méd., Paris **82**:120, 1919.

9. Thévenot, L.: De l'actinomycose du cœur et du péricarde, Bull. méd., Paris **17**:507, 1903.

TABLE 1.—*Actinomycosis of the Heart by Direct Extension*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1. Bastenie and others: Scalpel **86**: 1121,* 1933	Base invaded by granulation tissue; adhesion of layers	Cherry-sized nodule, in direct contiguity with pericardial lesion, occupies almost entire thickness of wall	Not involved	Lung	Direct extension to heart, wall of chest and pleura; amyloidosis of liver, spleen and kidneys	Man aged 38; cough, dyspnea, pain in chest and hemoptysis; edema, ascites and albuminuria due to amyloidosis; no congestive heart failure
2. Bates, R.: Lancet **1**: 571, 1933	Both layers thickened, adherent and containing abscesses (largest abscess 9 by 5 cm.)	Not involved	Not involved	Upper lobe of right lung	Extension to anterior mediastinum, wall of chest and pericardium	Age and sex not given; congestive heart failure (no details)
3. Benda, C.: Deutsche med. Wchnschr. **26**: 70, 1900	Involved by actinomycosis (exact details not stated)	Abscess in wall of right auricle	Perforated by abscess of right auricle	Lung	Extension to pleura and to pericardium, with invasion and thrombosis of the coronary vein of the heart, resulting in metastatic abscesses in kidneys and peritoneum	Diagnosis, pulmonary tuberculosis (no further details in report)
4. Cockburn, T. J.: Brit. M. J. **1**: 641, 1936	Shaggy fibrinous exudate and fibrin-containing effusion with actinomycetes	Apparently not involved	Apparently not involved	?	Multiple actinomycotic hepatic abscesses (no further details)	Woman aged 30; acute abdominal symptoms; later fever and vague intestinal disturbance; dysphagia, terminally
5. Edwards, A. C.: Am. J. Dis. Child. **41**: 1419 (June) 1931	Obliterated (not stated if actinomycetes present, but there was actinomycotic process on both sides)	Abscesses in wall of right ventricle	Yellowish gray polypoid masses	Lungs	Extension to mediastinum and heart; heart enlarged	Boy aged 10; cough, pallor and progressive congestive heart failure, including ascites, edema and hepatosplenomegaly
6. Geering, W.: Ein Beitrag zur geschwulstmässigen Aktinomycose des Herzens, Inaug. Dissert., Zurich, 1920 (?)	Thickened and completely adherent	Right auricle and ventricle thickened by large mass of actinomycotic tissue	Perforated in right ventricle by actinomycotic mass	(Unknown) Oldest lesion in anterior mediastinum	Direct extension to heart from mediastinum; multiple fistulas in wall of chest involving sternum; miliary spread to lungs	Woman aged 56; onset with pleuritis and pericarditis, followed by formation of sternal fistulas; progressive symptoms of congestive heart failure; enlarged heart, cyanosis, dyspnea, ascites, large liver and anasarca; sudden death due to heart disease
7. Genther, W. M., and Pendleton, R. K.: New York State J. Med. **32**: 1283, 1932	Abscesses on inner surface of parietal layer, which is adherent to left lung; small amount of fluid	Not involved by actinomycosis; microscopic examination showed acute suppurative myocarditis	Not involved	Left lung	Extension to wall of chest and pericardium	Man aged 30; pulmonary symptoms; died of hemoptysis
8. Hanau, A.: Cor.-Bl. f. schweiz. Aerzte **19**: 165, 1889	Sac obliterated; on separation, typical actinomycotic abscess and granulation tissue	Not involved	Not involved	Left lung	Rupture into superior vena cava	Woman aged 40; cough, fever, sweating, hemoptysis, enlarged heart and pericardial friction rub; no congestive heart failure
9. Harbitz, F., and Grondahl, N. B.: Beitr. z. path. Anat. u. z. allg. Path. **50**: 193, 1911 [case 1, p. 198]	Fibrinopurulent pericarditis due to actinomycosis	Actinomycotic myocarditis (details not given)	Not involved	Right lung	Wall of chest and peritoneum also involved; renal abscess	Man aged 26; chronic pulmonary symptoms; bloody sputum
10. Harbitz and Grondahl, case 10	Purulent pericarditis	Abscesses	Not involved	Lung	Empyema and abscess in wall of chest; extension to anterior and posterior mediastinum, liver and vertebrae	Boy aged 14; hemoptyses and empyema
11. Heinzelman, G.: Beitr. z. klin. Chir. **39**: 547, 1903 [case 43]	Actinomycotic nodules, some containing pus, on epicardium	Not involved	Not involved	Left lung	Extension to wall of chest, pleura, mediastinum and pericardium	Man aged 39; chronic productive cough, night sweats, abscess in wall of chest; no congestive heart failure
12. Hoover, C. A. (unpublished case), cited by Ruhräh, J.: Ann. Surg. **30**: 438, 1899	Completely adherent; with actinomycotic tubercles	Not involved	Not involved	Neck	Extension to mediastinum and left pleura, peribronchial and retroperitoneal glands, liver, spleen, kidneys, pancreas, stomach, duodenum and transverse colon	Man aged 43; chronic abscess of neck, on left side near angle of jaw; persistent sinus; abdominal pain, diarrhea and vomiting

13. Kissling: München. med. Wchnschr. **56**: 207, 1909 [case 1]	Pericarditis (exact details not given)	Involved	Actinomycotic endocarditis (details not given)	Mediastinum	Considerable involvement of mediastinal glands; extension to left innominate vein and left auricle; metastases to lungs, kidney, liver, spleen, brain and body wall	Girl aged 12; fever, unproductive cough, multiple cutaneous abscesses; progressive congestive heart failure
14. Köhler: Berl. klin. Wchnschr., 1884, p. 415. König, K. A.: Ein Fall von Actinomycosis hominis, Inaug. Dissert., Berlin, M. Niethe, 1884	Completely adherent; contains pus	Numerous abscesses	Not involved	Sternum	Direct extension to mediastinum and pericardium; multiple abscesses in pleurae, thyroid gland, spleen, liver, kidneys, colon, brain, body wall and oral mucous membranes	Woman aged 31; rapidly growing sternal tumor after blow; diagnosed as glanders; abscesses and ulcers all over body; heart entirely normal clinically except rapid rate and systolic metallic sound over apex; died in collapse
15. Koschlakow, 1885, cited by Illich, A.: Beitrag zur Klinik der Aktinomycose, Vienna, J. Safář, 1892, p. 95	Concretio cordis; many areas of pus containing actinomycetes in adhesions between layers	(Not mentioned)	(Not mentioned)	Left lung	Extension to pleura (no further description)	Man aged 22; picture of chronic pneumonia; died with ascites
16. Letulle, M., and Hufnagel, M.: Bull. Acad. de méd., Paris **82**: 120, 1919	Completely obliterated; infiltrated by actinomycotic tumor; forms one common mass with diaphragm	Walls of all four chambers invaded by actinomycotic tumor mass	Invaded by tumor mass in right auricle and ventricle; hyperplastic actinomycotic endocarditis	Esophagus	Direct extension to mediastinum and pericardium, then to base of right lung; bilateral pleural effusions; heart and inferior vena cava invaded from pericardium; tumor in lumen of inferior vena cava	Man aged 34; onset with pleurisy and bronchitis; chronic nonproductive cough and dyspnea; poor cardiac sounds, tachycardia, congestive heart failure with progressive edema
17. Meier, cited by Werthemann, A.: Virchows Arch. f. path. Anat. **255**: 734, 1925	(Obviously involved from general description; details not given)	Right and left auricles involved	Perforated in both auricles	Sternum	Direct extension to heart, pleura and lungs; metastases to liver, kidneys, spleen, intestine and skin	No details given
18. Münch, A.: Cor.-Bl. f. schweiz. Aerzte **18**: 234, 1888	Completely adherent; multiple actinomycotic abscesses present	Multiple abscesses in right auricle and both ventricles	Subendocardial nodules in both ventricles	Right lung	Extension to pleura; intracanalicular extension to both lungs by rupture into bronchus; direct extension to posterior mediastinum and vertebral column, then to pericardium and heart; heart most extensively involved of all organs, gross weight 714 Gm.; extensive pleuropericardial adhesions; emboli from coronary vein of heart to right testis and jejunum	Man aged 29; pulmonary symptoms (cough, fever, wasting); abscesses of chest wall; pyemia; sudden cardiac paralysis; no definite congestive heart failure
19. Paetzold, P.: Frankfurt. Ztschr. f. Path. **16**: 415, 1914-1915	Partly obliterated, with loculated pus and necrotic actinomycotic nodules on surfaces	Left ventricle and interventricular septum with multiple actinomycotic nodules, some partly necrotic; similar nodules in walls of both auricles, with polypoid formation	Rupture of auricular lesions into cavities	Right lung	Direct extension to pericardium, thence to myocardium and general circulation; metastases to brain, skull, myocardium, left lung, thyroid gland, liver, spleen, kidneys, small intestine and right femur; esophagus not involved	Boy aged 12; onset with general ill health, empyema and perforation of wall of chest; persistent cough and discharging sinus; other fistulas developed; death due to cachexia with anasarca; no dyspnea or hepatic enlargement
20. Ponfick, E.: Die Aktinomycose des Menschen, Berlin, A. Hirschwald, 1882 [case 3]	Completely obliterated; greatly thickened, due to actinomycotic granulation tissue, with many necrotic areas	Extensive involvement of wall of right auricle and ventricle by actinomycotic granulation tissue; apex of left ventricle also involved	Penetrated by massive tumor of actinomycotic tissue in right auricle and ventricle involving tricuspid valve	Probably right thumb	Extension, apparently through phlebitis of arm, to mediastinum; extensive abscess in prevertebral tissues; extension to deep tissues of neck with formation of a fistula on the left side; perforation into lumen of left internal jugular vein with apparent implantation on endocardium of right side of heart; bilateral pleurisy; multiple metastases to lungs; nodules in spleen and brain; esophagus involved but not perforated	Woman aged 45; onset, three years ante mortem, after cut on right antemortem, after cut on right ing entire right arm; general wasting; abscesses in left jugular area; pain and swelling in interscapular area; chronic cough terminally

TABLE 1.—*Actinomycosis of the Heart by Direct Extension—Continued*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
21. Ponfick, case 5	Filled with half liter of pus, parietal layer involved by actinomycotic nodules; covered with fibrin	Left ventricular wall near apex replaced by actinomycotic tissue	Not involved	Left lung	Extension to posterior mediastinum and retroperitoneal tissues; involvement of diaphragm, spleen and left wall of chest	Male patient, age not given; pain in left side of chest, cough and vomiting; death due to congestive heart failure (enlarged liver, anasarca, orthopnea)
22. Rutimeyer, L.: Berl. klin. Wchnschr. **26**: 45, 1889; Cor.-Bl. f. schweiz. Aerzte **19**: 234, 1889	Completely obliterated; large abscess present over posterior surface of right auricle; multiple small actinomycotic abscesses	Not involved	Not involved	Left lung	Extension to pericardium, pleura and wall of chest; generalized enlargement of heart, with hypertrophied left ventricle	Woman aged 22; chronic cough, pain in chest and fever; abscess of left wall of chest requiring incision; death due to congestive heart failure
23. Sauerbruch, F.: Die Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1925, vol. 2, p. 262	Involved by actinomycosis (no details)	Base of heart involved (no details)	(Not mentioned)	Wall of chest	Widespread fistula in wall of chest	Boy aged 14 (case is personal observation of author; no details)
24. Schmorl, G.: Jahresb. d. Gesellsch. f. Nat. u. Heilk., 1913, p. 161	(Not described)	Both auricles involved	Polypoid growths in both auricles	Right lung	Extension to wall of chest and by way of hilus to heart; disseminated actinomycosis of all organs	Boy aged 14 (clinical details not given)
25. von Schrötter, L.: Internat. Beitr. z. inn. Med. **1**: 535, 1902	Completely obliterated and adherent to pleura bilaterally, due to actinomycotic granulation tissue	Left ventricle and both auricles contain actinomycotic granulation tissue and areas of pus; most of cardiac muscle replaced	Apparently not involved	Left pleura	Extension to mediastinum, right pleura, diaphragm and left wall of chest; lungs apparently not involved	Man aged 49; actinomycosis of heart suspected clinically; onset with pain in left side of chest, then abscess and fistulas; later, cough, cardiac irregularity and pericardial friction rub; no congestive heart failure, although death was apparently due to circulatory collapse
26. Tubbs, O. S., and Turner, J. W. A.: St. Barth. Hosp. J. **44**: 184, 1937	Filled with thick green pus; fibrinous exudate over entire surface; pure culture of actinomycetes obtained during life and post mortem	(Not mentioned)	(Not mentioned)	Right lung and pleura	Direct extension to wall of chest and to retroperitoneal tissues behind right kidney	Man aged 35; pain in right lower part of chest; cough, fever, abscess of wall of chest; sudden onset of dyspnea; roentgenogram, pericardial effusion; death with congestive heart failure
27. Werthemann, A.: Virchows Arch. f. path. Anat. **255**: 719, 1925	Completely obliterated; left pleuropericardial adhesions, all due to actinomycetes	Abscesses in right auricle and tip of right ventricle; actinomycotic granulation tissue in left auricle	Ulcerated in both auricles, over underlying myocardial lesion	Left lung, lower lobe	Extension to left pleura, tracheal lymph nodes, mediastinum and pericardium; multiple metastatic abscesses in both lungs, myocardium, spleen, kidneys, small intestines, brain and subcutaneous tissue	Man aged 36; fever, pain in chest and cough; multiple subcutaneous abscesses; pericardial friction rub; no congestive heart failure; death due to sepsis and cachexia
28. Cornell and Shookhoff, case 1 (N. C.)	Completely obliterated by actinomycotic granulation tissue	Both ventricles and auricles replaced to large extent by actinomycotic granulation tissue	Subendocardial fibrosis in left ventricle; not involved by actinomycosis	Esophagus	Direct extension to posterior mediastinum, pericardium, myocardium, base of right lung, pleura and diaphragm	Man aged 30; picture of congestive heart failure with fever; diagnosed clinically as rheumatic heart disease; death due to streptococcal pneumonia, with empyema
29. Cornell and Shookhoff, case 3 (A. T.)	Completely obliterated by dense adhesions containing small collections of pus	Entire thickness of right auricle involved by necrotic actinomycotic tissue	Polypoid excrescences in right auricle, over myocardial lesion	Right lung, lower lobe	Direct extension to right pleura, wall of chest, posterior mediastinum, heart, muscles of esophagus, diaphragm, right kidney and paravertebral tissues down to sacrum; amyloid disease of spleen	Boy aged 7; fever, vomiting and loss of weight, then right-sided empyema partially perforating wall of chest; enlargement of heart; death due to progressive anemia and cachexia

[a] Volume incorrectly paged; the page should be numbered 1661.

a little more pronounced than usual in the statistics just presented.

PATHOLOGIC PICTURE OF CARDIAC ACTINOMYCOSIS

Cardiac Involvement by Direct Extension of the Process to the Pericardium (*table 1, 29 cases*).—In 15 of the 24 cases in which details were given complete obliteration of the sac was reported. The layers of the pericardium were involved by actinomycotic granulation tissue, in which suppurative foci were usually present. In 2 instances the pericardial layers were similarly involved but the sac was only partially obliterated. In 1 of these 2 a collection of pus filled the portion of the sac which was not obliterated. There were 5 other instances in which fibrinopurulent pericarditis was noted, and in at least 1 of these the amount of pus was great, half a liter (Ponfick, case 5). In the remaining 2 instances only one of the pericardial layers was involved and there was no effusion.

The myocardium was invaded in 20 of 29 patients with direct cardiac involvement. The process consisted of infiltration with actinomycotic granulations, formation of multiple nodules of such tissue or development of one or more abscesses in the substance of the cardiac muscle.

The process reached the endocardium in 12 of the 29 patients, and in 3 of the 12 it gave rise to polypoid excrescences extending into the cavity of the heart. In 6 instances the process actually perforated the endocardium with resultant pyemia.

The primary site of the actinomycosis was stated in the reports of 27 cases. In 19 instances it was the lungs and pleura. Other primary sites were the wall of the chest, the esophagus, the mediastinum, the neck and the thumb. Spread of the process in all instances was either through the mediastinum or from the pleura directly to the pericardium.

As might be expected, involvement of the large veins was not rare. The superior vena cava, the inferior vena cava, the innominate veins, the internal jugular veins and the coronary veins were affected in different instances and in some the thrombophlebitis gave rise to pyemia.

Associated involvement of contiguous organs, aside from the primary site, was, of course, present. The organs already mentioned as primary sites were in other instances secondarily involved. The infection has also been reported as spreading to the spine and upper abdominal organs.

The esophagus was obviously the primary site in only 1 instance [8] other than that reported in case 1 (N. C.). In 2 other instances the esophagus was involved without perforation.

Pyemic Cardiac Involvement (*table 2, 19 cases*).—In the 19 cases tabulated, the myocardium was involved in 17 instances, there being multiple foci in 11 and a single focus in 6. Most commonly the involvement was in the ventricular walls, the right and left sides being involved with equal frequency.

In 3 instances there was definite invasion of the pericardium from the myocardium. In 2 of the 3 instances there were extensive adhesions, containing foci of actinomycosis. In the other the condition was purulent actinomycotic pericarditis. In the remaining 16 instances the pericardium either was not involved or was involved only by reaction to an underlying myocardial process, resulting in adhesions, fibrinous deposits, excess fluid or a combination of these.

The endocardium was usually intact. In 2 instances the underlying myocardial lesion had perforated it. In 1 instance (Dean) the involvement was limited to the endocardium of the mitral valve and apparently resulted from direct implantation by way of the blood.

There were 2 other instances in which actinomycotic endocarditis occurred without involvement of the other tissues of the heart. One was that reported by Uhr, in which the clinical and pathologic features of subacute bacterial endocarditis were presented. The second was that of Jervell [10] referred to by Uhr, in which acute endocarditis was superimposed on an old rheumatic lesion.

Reactive Pericarditis (*table 4, 12 cases*).—In 12 instances there was definite actinomycotic disease in tissues in contiguity with the pericardium but the fungus was not demonstrated in the pericardium itself.

The pathologic conditions varied. In some instances there was only a fibrinous deposit; in others clear or fibrinopurulent effusions were present, and in still others there was complete obliteration of the sac.

The primary site of the process was the lungs in 10 instances and the esophagus in 2.

In summary it may be said that actinomycosis involves the heart either by direct extension from a continguous organ or through the blood. When involvement is by direct extension the infection usually gains access to the pericardial sac and in most instances completely obliterates it. Usually the myocardium is involved, and not infrequently the infection progresses to involve

10. Jervell, O.: Leptothrix in the Blood of a Case of Malignant Endocarditis, Norsk mag. f. lægevidensk. **83**:36, 1922.

* Volume incorrectly paged; the page should be numbered 1061.

TABLE 2.—*Actinomycosis of the Heart Due to Pyemia*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1. Abee, C.: Beitr. z. path. Anat. u. z. allg. Path. **22**: 132, 1897 [case 3, p. 146]	Parietal layer adherent to lungs; sac contained 100 cc. of pale yellow fluid; local thickening and fibrin over abscess of myocardium	Abscess in wall of right ventricle	Intact; merely elevated by underlying myocardial abscess	Esophagus	Extension to vertebrae, with perispinal abscess; involvement of wall of chest, mediastinum and lungs; metastases to brain and meninges	Boy aged 14; chronic cough, dyspnea, pain in chest and fever; death due to sepsis; no congestive heart failure
2. Anders, H. E.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **40**: 1, 1925	Contained a few cubic centimeters of slightly turbid fluid	Multiple abscesses	Not involved	Appendix	Local extension to peritoneum; metastases to liver, kidneys, lungs and brain	Man aged 38; pain in lower abdominal region and vomiting; operation for appendicitis; recurrent abscess in right lower quadrant; septic course
3. Barbier and others: Lyon méd. **161**: 212, 1938	Contained a small amount of thick fluid; visceral layer thickened, due to underlying nodules	Three large actinomycotic nodules	Not involved; merely elevated by underlying myocardial nodules	Lungs	Extension to wall of chest; metastases to kidney, spleen and skeleton	Man aged 37; onset like pneumonia, followed by chronic pulmonary symptoms and fistulas in the wall of the chest; no evidence of involvement of heart clinically
4. Benda, C.: Deutsche med. Wchnschr. **26**: 70, 1900	Not involved	Tiny actinomycotic nodule in wall of left ventricle	Not involved	Cecal region	Abscess in cecal region, with extension to abdominal wall, liver, portal vein and inferior vena cava through hepatic vein; pyemic abscesses in lungs and kidneys	Boy aged 15; operated on for appendicitis with temporary improvement; septic picture and death
5. Bruun, E.: Hospitalstid. **81**: 16, 1938	Adherent (not stated whether completely)	Multiple abscesses	Not involved	(Undetermined)	Pyemic abscesses in lungs, liver, spleen and kidneys	Man aged 27; chronic pulmonary disease with fever, cough and dyspnea; multiple subcutaneous abscesses; pericardial rub; no congestive heart failure
6. Carrión, A. L.: Puerto Rico Pub. Health & Trop. Med. **13**: 367, 1938	Single thick adhesion between pericardial layers	Multiple abscesses	Not involved	Lung	Abscesses in kidneys, liver, spleen, thyroid gland, brain, tonsil and muscles	Boy aged 8; pulmonary symptoms, sinus of the wall of the chest; septic course; heart normal clinically
7. Dean, G.: Brit. M. J. **2**: 1303, 1912	Not involved	Not involved	Warty vegetation on auricular aspect of mitral valve; microscopically, definite actinomycosis	Appendix	Pyemic spread to liver and lungs (no other details)	Patient (sex not given) aged 22; gangrenous appendix removed; abscess in wall of chest, treated surgically (no further details)
8. Fellinger, K., and Salzer, G.: Virchows Arch. f. path. Anat. **286**: 638, 1932	Not involved	Grossly normal; microscopically, actinomycotic nodule in left ventricular wall	Rupture of myocardial nodule into chamber of left ventricle, with formation of thrombus containing actinomyces	Right lung	Metastases to brain, thyroid, liver, spleen, kidneys and spine; multiple abscesses of body wall, generalized	Man aged 59; cough and expectoration; septic picture with multiple subcutaneous abscesses
9. Freed, C. F., and Light, F.: Pennsylvania M. J. **36**: 25, 1932	200 cc. of turbid yellow fluid in sac; parietal and visceral layers have fibrinopurulent green exudate; pleuropericardial adhesions on the left side	Multiple abscesses	Perforated by abscess in right ventricle	Lungs	Extension to wall of chest; empyema on left side and bronchial fistula; metastases to liver and spleen; heart normal in size	Man aged 39; cough, expectoration and abscesses in wall of chest; septic picture; heart normal clinically; cultures of blood positive for actinomycetes; organisms found also in sputum, urine and pus

	Small amount of clear fluid in sac; no evidence of actinomycetes	Two yellow actinomycotic nodules at base of tricuspid valve	Wrinkled over nodules, but not perforated	Right lung	Perforation of diaphragm from base of right lung; invasion of liver	Man aged 39; operation for acute pain in right upper quadrant of abdomen; jaundice; persistent fistula draining pus containing actinomycetes; heart normal clinically
10. Fütterer, G.: Virchows Arch. f. path. Anat. **171**: 278, 1903						
11. Harbitz, F., and Grondahl, N. B.: Beitr. z. path. Anat. u. z. allg. Path. **50**: 193, 1911 [case 5, p. 199]	Not mentioned	Multiple actinomycotic abscesses	Not involved	Neck and upper lobe of right lung	Extension to sternum and anterior mediastinum; metastases to kidneys, liver, lungs, central nervous system, tongue and body wall	Man aged 22; multiple sinuses in neck with pyemia; epileptiform seizures
12. Israel, O.: Berl. klin. Wchnschr. **25**: 71, 1888	Sac not involved; subepicardial actinomycotic nodule	Normal except for subendocardial nodules in apex of left ventricle	Not involved, except as noted under myocardium	(Not known)	Actinomycotic abscess between stomach, spleen and diaphragm; metastatic abscesses in spleen, liver, kidneys and femur	Woman aged 44; presenting symptoms; abscess of inner aspect of left thigh
13. Kashiwamura, S.: Virchows Arch. f. path. Anat. **171**: 257, 1903 [case 4]	Fibrinous exudate on both layers; 700 cc. of bloody fluid in sac	Actinomycotic nodules in walls of both ventricles	Not involved	Lung	Pyemic abscesses of lungs, spleen and kidneys; bilateral empyema; extension to wall of chest, involving ribs and vertebrae	Man aged 29; cough, fever and empyema necessitatis; multiple subcutaneous abscesses; heart normal clinically
14. Kasper, J. A., and Pinner, M.: Arch. Path. **10**: 687 (Nov.) 1930	Almost completely obliterated; parietal layer thickened; contained yellow foci	Multiple actinomycotic abscesses in walls of both ventricles, involving almost entire thickness	Not involved	(Not determined)	Multiple abscesses in lung, mucosa of ileum, right arm and thigh; actinomycotic colonies in pulmonary and systemic vessels (microscopic examination)	Man aged 30; cough, pain in the chest and fever; congestive heart failure with dyspnea, edema, ascites and congestion of liver and spleen
15. Kramer, P. H.: Nederl. tijdschr. v. geneesk. **81**: 1900, 1937	Not involved	Multiple actinomycotic abscesses	Not involved	Lung	Extension to wall of chest; pyemic abscesses in kidneys and testes	Man aged 36; fever and a pyemic course
16. Roeder: Zentralbl. f. Chir. **32**: 923, 1905	(Not mentioned)	Single myocardial nodule	(Not mentioned)	Lung	Actinomycotic abscesses in kidney	(No clinical details)
17. Schwerdtfeger, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **43**: 336, 1933 [case 1, p. 344]. Bode, H. G.: Arch. f. Dermat. u. Syph. **167**: 550, 1933	Completely adherent; contained actinomycotic nodules	Not involved	Not involved	Left lung	Metastases to skin, left kidney and pericardium; empyema on the left side (actinomycotic)	Man aged 23; treated for pulmonary tuberculosis (left lung); later multiple cutaneous ulcers diagnosed as tuberculosis, until postmortem examination showed them to be actinomycotic; death due to toxemia
18. Schwerdtfeger, case 2	Epicardium extensively involved by actinomycotic granulation tissue; 350 cc. of pus in sac, due to rupture of myocardial abscesses	Numerous actinomycotic abscesses in wall of right ventricle	Thrombotic deposit over endocardium of right ventricle (exact nature not mentioned)	Left side of neck	Bronchopneumonic extension to lungs; actinomycotic abscess in right lobe of thyroid	Man aged 29; operated on for actinomycosis of neck; became moribund shortly afterward (no further details)
19. Shapiro, P. F.: Arch. Path. **12**: 397 (Sept.) 1931	(Not mentioned)	Small abscess in wall of left ventricle	Pus-filled polypoid masses projecting between papillary muscles of mitral valve	Upper lobe of right lung	Metastases to liver, kidneys, thyroid, brain, skull and subcutaneous tissue; pleurisy on the right side with collection of pus near apex; actinomycotic thrombophlebitis of renal vein	Man aged 45; cough, pain in chest, fever, bloody sputum and multiple subcutaneous abscesses; death due to sepsis

In 2 cases there was pyemic involvement of the heart in addition to involvement by direct extension; Paetzold, case 19 and Werthemann, case 27 (table 1).

and perforate the endocardium, with resultant pyemia. At times, however, the only change is a pericardial reaction without actual invasion.

When the heart is affected by way of the blood stream the myocardium, rather than the pericardium, is the site of primary involvement. Extension to the pericardium and/or the endocardium occurs in a few instances. Rarely the result of pyemic involvement is an endocardial vegetation alone.

Histologically, actinomycotic lesions in the heart do not differ from those found elsewhere in the body. They are a combination of granulation tissue and abscess. At times the former type of lesion predominates, resulting in the formation of tumor-like masses of tissue. In other instances abscess formation is more prominent and large collections of pus may be formed.

pericardium, in one or another form, was reported.

As might be anticipated, in pyemic cardiac involvement the general picture of pyemia overshadowed the manifestations of involvement of the heart. In one report the classic picture of subacute bacterial endocarditis was presented. Of 19 patients with pyemic involvement of the heart 1 (Kasper and Pinner) exhibited congestive heart failure and another (Bruun) had a pericardial friction rub. The other 17 lacked cardiac manifestations.

TABLE 3.—*Actinomycosis of the Heart, Pathogenesis Not Clear*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1. Kissling: München. med. Wchnschr. **56**: 207, 1909 [case 2]	(No details given)	Myocarditis actinomycotica (Exact details not given)	Endocarditis actinomycotica	Mediastinum (?)	Lesion in mediastinal glands breaking into superior vena cava with metastatic foci in lungs, kidney, brain and skin	Man aged 43; fever, constitutional symptoms and signs of dry pericarditis and of pleurisy on the left side
2. Lutz, R., cited by Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 462	Involved (no details given)	Multiple small abscesses in wall of right ventricle	Not involved *	Heart	No involvement outside heart and pericardium *	Woman aged 58 (no details available)
3. Paltauf, R.: Wien. klin. Wchnschr. **3**: 487, 1890	300 cc. of foul pus, containing actinomycotic granules in sac; both layers contained actinomycotic nodules	Isolated, actinomycotic tumor in wall of right ventricle	Vegetations overlying and continuous with myocardial tumor	Lung	Multiple actinomycotic foci in both lungs, metastatic as well as primary; difficult to tell whether heart was involved directly or by pyemic spread	Woman aged 31; fever; clinical diagnosis of pericardial exudate
4. Uhr, N.: Arch. Int. Med. **64**: 84 (July) 1939	Not involved	Not involved	Large, soft, friable, yellowish vegetation on mitral valve, spreading to lining of left ventricle	(Unknown)	Clusters of abscesses and nodules in lungs; confluent purulent bronchopneumonia (not stated to be actinomycotic lesions)	Man aged 24; fever, chills, sweats, bloody sputum, petechiae, gangrene of the skin and hemiplegia; progressive, apical systolic murmur; cultures of blood contained Actinomyces bovis on four occasions
5. Cornell and Shookhoff, case 2 (J. R.)	Completely adherent, with single collection of pus over right ventricle	Multiple abscesses	(Not examined)	Left lung	Multiple abscesses in lungs; extension to wall of chest; single abscess of kidney; amyloidosis of liver, spleen and kidneys	Boy aged 11; pain in the chest; productive cough, recurrent abscesses of left wall of chest; septic course; death due to toxemia; no cardiac signs

* According to Kasper and Pinner,[4] there was embolic involvement of the lung; this suggests that the endocardium may have been involved.

CLINICAL PICTURE

Of the 68 reports of cases studied, clinical descriptions were given in 60. In 23 of these clinical evidence of disease of the heart and/or

Aside from the cases of pyemic involvement and the doubtful cases listed in table 5, there are 46 cases. Of these, clinical descriptions are available for 41. In 21 of these there was clinical evidence of disease of the heart. Twelve patients showed frank congestive heart failure. In 3 patients a pericardial friction rub was heard. For 2 others, 1 with congestive failure, the clinical diagnosis was pericarditis with effusion, the basis for which is not given in detail. Two patients died with circulatory collapse. Of

TABLE 4.—*Actinomycosis with Reactive Pericarditis*

Author	Pericardium	Myocardium	Endocardium	Primary Site of Infection	Route of Progression	Clinical Data
1. Abee, C.: Beitr. z. path. Anat. u. z. allg. Path. **22**: 132, 1897 [case 2, p. 137]	Numerous tenuous and some firmer adhesions between layers	Not involved	Not involved	Esophagus, near cardia	Extension from mediastinum toward pericardium; perforation and thrombosis of inferior vena cava, with pyemic abscesses in lungs, liver, spleen and meninges; direct extension to vertebrae and sternum	Man aged 40; hemoptysis and dyspnea; death due to sepsis; no congestive heart failure
2. Adler: Deutsche med. Wchnschr. **16**: 596, 1890	Sac completely obliterated	Not involved	Not involved	Right lung	Extension to right pleura and wall of chest and to anterior mediastinum, with perforation of superior vena cava	Woman aged 51; cough, sputum and perforation of wall of chest; heart normal clinically
3. Anderson, A. V. M., and Trinca, A. J.: M. J. Australia **2**: 332, 1932	Adherent to lungs and heart but no actinomycotic infiltration	(Not mentioned)	(Not mentioned)	Right lung and pleura	Extension to wall of chest, left lung, left elbow, kidneys, lumbar vertebrae, liver and subcutaneous tissues	Woman aged 33; cough and abscess of right wall of chest at the age of 17; improved with potassium iodide therapy and drainage; recurred fourteen years later, with pyemic abscesses and respiratory symptoms; heart normal clinically; pleurisy and pericarditis diagnosed clinically
4. Aphalo, J.: Actinomicosis thorácica, Thesis, Buenos Aires, 1915, p. 139	Adherent, but layers easily separated	Not involved	Not involved	Right lung	Both kidneys and lumbar vertebrae involved	Man aged 49; cough, pain in chest, fever, multiple subcutaneous abscesses; died with congestive heart failure
5. von Barsacz, R.: Arch. f. klin. Chir. **68**: 1050, 1902	Sac completely obliterated	Not involved	Not involved	Esophagus	Extension to mediastinum, lungs, sternum and wall of chest	Man aged 45; dysphagia, fever and cough; no congestive heart failure
6. Bigland, A. D., and Sergeant, F. C. H.: Brit. M. J. **2**: 61, 1923	At operation, thin fluid found in sac; surfaces had bread-and-butter appearance; discharge later, thick and yellow; no actinomycetes found	(Not accessible)	(Not accessible)	Right lung	Actinomycetes in discharge obtained at thoracotomy	Man aged 22; picture of empyema; rib resection done; pericardial effusion suspected; proved by exploratory operation; recovery after siege of congestive heart failure
7. Miller, S. R., and Merkel, W. C.: M. Clin. North America **18**: 1725, 1935	Adherent to anterior wall of chest; sac contained 250 cc. of clear fluid	Not involved	Not involved	Left lung	Extension to pleura of the left side and to right lung	Man aged 34; attack of precordial pain radiating to left arm; then fever, cough, blood-tinged sputum and sweats; persistent deep pain in left side of chest; died of pulmonary hemorrhage
8. Moosbrugger, P.: Beitr. z. klin. Chir. **2**: 384, 1886 [case 11]	Completely obliterated by easily separated adhesions (microscopic details not given)	Not involved	Not involved	Lungs	Multiple actinomycotic nodules throughout both lungs; extension to pleura of left side and to left anterior wall of chest, with perforation	Man aged 39; chronic bronchitis; swelling and ulceration of left anterior wall of chest; dyspnea and edema, for which digitalis was given; asphyxial death
9. Poncet, A., and Bérard, L.: Traité clinique de l'actinomycose humaine, pseudo-actinomycoses et botryomycoses, Paris, Masson & Cie, 1898 [case 94, p. 239]	Completely adherent and thickened	(Not mentioned)	(Not mentioned)	Left lung	Extension to pleura and wall of chest	Man aged 48; fever; abscess of left wall of chest; death with cachexia
10. Ponfick, E.: Die Aktinomycose des Menschen, Berlin, A. Hirschwald, 1882 [case 1]	Fibrinopurulent pericarditis; no actinomycetes	Not involved	Not involved	Left lung	Extension to mediastinum and wall of chest	Man aged 45; pleurisy on left side, followed by persistent pain, productive cough and dyspnea; abscess of wall of chest, with perforation
11. Shiota, H.: Deutsche Ztschr. f. Chir. **101**: 289, 1909	200 cc. of cloudy, fibrinous fluid; surface covered with fibrin; adhesions to right lung	(Not mentioned)	(Not mentioned)	Left lung	Extension to pleura, wall of chest and mediastinum (abscess contiguous to pericardium), also to right lung, vertebrae and meninges	Boy aged 11; onset with pain in left side of chest and fever; abscess of wall of chest and fistulas; died in cachexia
12. Thiersch and Bahrdt, cited by Israel, J.: Klinische Beiträge zur Kenntnis der Aktinomykose des Menschen, Berlin, A. Hirschwald, 1885 [case 20, p. 48]	Fibrinous deposit on both layers	Not involved	Not involved	Left lung	Extension to pleura and mediastinum, with fistulas to right of sternum	Man aged 50; cough, sputum, fever and hemoptysis; abscess of left wall of chest with perforation; death due to sepsis

patient (Tubbs and Turner, table 1) showed cardiac enlargement, and 1 exhibited a "peculiar systolic metallic sound." A "cardiac irregularity" is reported for 1 patient (von Schrötter, table 1), and in this patient actinomycosis of the heart was clinically suspected.

Cardiac murmurs occurred in our patient N. C. and in 1 with subacute bacterial endocarditis (Uhr, table 3).

Electrocardiographic tracings were available for only 2 patients (N. C. and A. T. in this article). In the tracing for A. T. there was deviation of the axis to the left, while the electrocardiogram for N. C. showed disturbance of intraventricular conduction, deviation of the axis to the right, tachycardia and changes in the P wave and T wave (fig. 1).

TABLE 5.—*Cases Reported as Instances of Actinomycosis of Heart but Diagnoses Not Adequately Established*

Author	Summary of Case
1. Hebb, R. G.: Proc. Roy. M. & Chir. Soc. **2**: 197, 1885-1888	Actinomycotic abscess of the liver, proved by microscopic examination, with a vegetation on the wall of the right auricle; cited by A. Illich (Beitrag zur Klinik der Aktinomycose, Vienna, J. Safář, 1892) as an example of actinomycosis of the heart
2. Naunyn, B.: Mitt. a. d. med. Klin. zu Königsberg 1888, p. 296	Small fresh excrescences on auricular surface of both leaves of the mitral valve; gray-yellow tiny deposit on aortic valve showed streptothrix microscopically; primary lesion undetermined; pia mater contained reddish-brown areas also showing streptothrix (microscopic examination); patient was a 17 year old girl with chorea, headaches and fever; apparently death resulted from chorea; reported as an example of actinomycosis of the brain and heart by Henry (J. Path. & Bact. **14**: 164, 1909). (The actual bacteriologic status of the fungus must remain indefinite, since actinomycosis in man was not fully identified until 1889)
3. Richter: Thesis, Kiel, 1901; cited by Hufnagel, L.: L'actinomycose du cœur, Thesis, Paris, no. 234, 1919, p. 16	(Mentioned as case of actinomycosis of heart; no details or description given by Hufnagel; original reference not available)

CLINICOPATHOLOGIC CORRELATION

Since in the reports of many cases the details which are available are extremely meager, conclusions as to the correlation of clinical and pathologic data cannot be drawn with statistical certainty. However, certain impressions are gained from a study of the tabulated cases.

Of the 60 patients for whom clinical facts were available, there were 13 in whom congestive heart failure occurred. Twelve of these showed complete obliteration of the pericardial sac. The remaining patient exhibited severe pericardial effusion. Only 3 of the 13 patients showed extensive involvement of the myocardium, and 7 showed no involvement of cardiac muscle. It would appear, therefore, that in the production of congestive heart failure due to actinomycotic infection pericarditis plays the major role. It must be added that a large pericardial lesion did not always produce congestive failure, since 17 patients with extensive pericardial involvement showed no signs of failure.

There were 4 instances of sudden fatal collapse. In all of these extensive myocardial as well as pericardial involvement was found. It would seem that sudden collapse in actinomycotic infection of the heart depends on extensive destruction of cardiac muscle. It must be pointed out that in Ponfick's third case (table 1) there were fairly widespread myocardial involvement and complete obliteration of the pericardium without any clinical manifestations of heart disease.

Murmurs were heard in only 2 patients. In the patient described by Uhr, presenting the picture of subacute bacterial endocarditis, a systolic murmur, increasing in intensity, was heard and at autopsy a vegetative mycotic lesion was found on the mitral valve. In our patient N. C., however, although definite presystolic and systolic murmurs were heard at the apex over a long period of time by several observers, no involvement of any valve was found.

In general it may be said that clinical evidence of heart disease due to actinomycosis is more apt to be lacking than present. It was found in 23 of 60 patients. Even extensive involvement may go undetected (Ponfick, case 3, in table 1). In those instances in which clinical manifestations of heart disease did occur, such manifestations almost always appeared late in the course of the disease. It is distinctly rare for the presenting picture to be primarily that of heart disease. This condition has been observed only in the patient described by Letulle and Hufnagel (table 1) and in our patient N. C., probably because these were the only 2 patients in whom the infection entered by way of the esophagus.

Actinomycetes may gain access to the thoracic cavity in four ways other than by the esophageal route: (1) aspiration of the organism into the lungs; (2) extension from a cervical process; (3) extension from an abdominal process, and (4) metastasis in the blood stream. With each of these types of invasion the early symptoms are those which are referable to the starting point of the infection, pulmonary symptoms, cervical abscesses, abdominal disturbances or symptoms of pyemia. In contrast, when the esophagus is the portal of entry there are no definite symptoms until the infection progresses farther. When it spreads anteriorly, into the mediastinum, the peri-

cardium is likely to be the first vital tissue involved. It is under these conditions that the illness will probably be ushered in with symptoms and signs referable to the heart. The possibility of infection of the thoracic area by way of the esophagus has been neglected by some writers in discussing actinomycosis. It should be kept in mind as a possible portal of entry and may well explain the condition reported by Lutz as primary actinomycosis of the pericardium and heart (table 3).

Obviously the diagnosis of actinomycosis of the heart will be missed in many instances. It should be remembered, however, that cardiac involvement is usually secondary to actinomycosis of the lungs, and the possibility of its occurrence as a complication in the latter disease should be kept in mind. This problem is of more than academic importance. Thoracic actinomycosis is not uniformly fatal. With the help of surgery, radiotherapy and sulfonamide drugs, and recently of penicillin, recovery has occurred in a considerable number of instances. In the treatment of thoracic actinomycosis the recognition of a complicating cardiac involvement may prove of practical value, as in the case reported by Bigland and Sergeant (table 4). In this instance it was possible to relieve surgically the effects of pericardial effusion, and the patient eventually recovered.

SUMMARY

Involvement of the heart in actinomycosis is rare.

Analysis of 3 new cases and of 65 others collected from the literature shows that the heart may be involved by direct extension of the infection from a neighboring organ (most commonly the lungs) or by metastasis through the blood.

Metastatic involvement rarely produces clinical signs. Of the patients in whom involvement of the heart is by direct extension, about half show clinical manifestations.

The most common clinical manifestation in cardiac actinomycosis is congestive heart failure. A pericardial rub was heard in 3 cases and cardiac murmurs in only 2.

CONCLUSIONS

In the production of congestive heart failure due to actinomycotic infection pericarditis plays the major role.

The diagnosis of cardiac actinomycosis is rarely made clinically, but it should be considered in every instance of pulmonary actinomycosis, especially since surgical relief of pericardial effusion may be indicated. Cardiac manifestations as the presenting symptoms of actinomycotic infection are rare. Such a picture has been described only once prior to the present report.

The possible routes by which actinomycetes may gain entry to the thoracic cavity are (1) aspiration of the organism into the lungs, (2) extension of a cervical infection, (3) extension of an abdominal infection and (4) metastasis in the blood. It is important to recognize that actinomycotic infection may gain access to the thorax by way of the esophagus. In such circumstances extension to the heart is likely to occur.

NOTE.—After the completion of this study there came to our attention the following case reported by A. C. Gose.[11]

A 53 year old man sprained his ankle on Oct. 17, 1939. Shortly thereafter an abscess developed over the ankle. After the abscess was incised a sinus remained and a second operation failed to clear up the infection. The presence of a cough, dyspnea and a septic fever led to the discovery of consolidation at the base of the left lung. A picture suggesting constrictive pericarditis developed. An electrocardiogram showed low voltage in all leads, and pericardiotomy revealed an adherent pericardium and an abscess. Postmortem examination revealed considerable pericardial thickening, with obliteration of the sac. The thickened pericardium contained numerous small sinuses and one large abscess cavity. The myocardium and endocardium were not invaded. The infection originated in the left lung and spread to the inferior mediastinum. The right leg and foot showed numerous sinuses due to actinomycosis. There were no other specific lesions.

The diagnosis in this case was made only after postmortem histologic study. This illustrates once again the difficulty in identifying actinomycosis of the heart clinically.

Another case of cardiac actinomycosis resulting from direct extension has also been found reported [12] since this article was submitted for publication.

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11. Gose, A. C.: A Case of Constrictive Pericarditis Due to Actinomycosis, Memphis M. J. **17**:56, 1942.

12. Lidbeck, W.: Actinomycosis: Report of Two Cases Showing Uncommon Clinical and Pathological Features, West. J. Surg. **50**:498, 1942 [case 2].

SICKLE CELL DISEASE

I. OBSERVATIONS ON BEHAVIOR OF ERYTHROCYTES IN SICKLE CELL DISEASE

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Sickle cell anemia is a specific and unique disease of growing importance, in that it is much more common than was previously suspected [1] and is more generally recognized. Adequate surveys [2] indicate that the sickle cell trait occurs in not lower than 7 per cent of all American Negroes and that the incidence may be considerably higher.[1a] The ratio of the symptomless sickle cell trait to the clinical sickle cell disease is not definitely known, but it may be as high as 9:1 [3] or even 7:1.[1c] Since the trait is hereditary and is dominant over the normal condition,[4] it is evident that any one of the 900,000 odd persons with sickling [1c] in the United States may transmit the full disease to his or her offspring. The total number of persons with sickle cell disease in this country, all of them doomed to ill health and probably abbreviated life expectancy,[5] is estimated at 135,000.[1c]

Sickling is a property inherent in the erythrocytes and not dependent on the other elements of the blood, although it is enhanced or inhibited by varying influencing environmental factors. Since the fundamental cause of the abnormality of the red cells is to be found in a dominant gene, it is improbable that the mystery of the cause of sickling will be entirely solved in a laboratory. Nevertheless, the investigation of the chemical and metabolic factors involved in the mechanism of sickling may shed considerable light on the behavior of the erythrocytes in this and in other diseases of the blood.

The specimens of blood used in our studies were obtained from a 21 year old male Negro with severe sickle cell disease who was observed at St. Luke's Hospital for seven months. Numerous clinical investigations and other special studies were conducted during this period of hospitalization and are to be reported separately. The purpose of this paper is to describe the results of studies on the behavior of the erythrocyte in sickle cell disease.

Sickle cell disease was manifested in this patient by periods of violent hemolytic activity ("crises") and there was present an intractable anemia of strictly normocytic and normochromic character. The red blood cell counts, hemoglobin values and readings of hematocrit volume never rose above 70 per cent of normal and were usually much lower. During one crisis, such massive hemolysis occurred that 37 per cent of the patient's existing red blood cell elements were destroyed within six days, as revealed by duplicate determinations. High concentrations of bilirubin and urobilin in the blood, reticulocytosis, normoblastosis and marked roentgenographic evidence of hyperplasia of the bone marrow all afforded evidence of an extreme degree of chronic hemolysis.

1. DEMONSTRATION OF SICKLING

The blood cells were studied by means of preparations of smears, chamber counts and hanging drops. Sickle cells appeared in all of these but remained few except when special methods were employed to encourage sickling. The standard procedure which was described by Emmel [6] in 1917 was modified by us to permit a more rapid sickling of the red cells. In all of our preparations sickling had progressed to completion within a maximum period of ninety minutes at

From the medical service of St. Luke's Hospital.

1. (*a*) Beck, J. S., and Hertz, C. S.: Standardized Sickle Cell Method and Evidence of Sickle Cell Trait, Am. J. Clin. Path. **5**:325, 1935. (*b*) Diggs, L. W., and Pettit, V. D.: A Comparison of the Methods Used in the Detection of the Sickle Cell Trait, J. Lab. & Clin. Med. **25**:1106, 1940. (*c*) Ogden, M. A.: Sickle Cell Anemia in the White Race, Arch. Int. Med. **71**:164 (Feb.) 1943.

2. (*a*) Graham, G. S., and McCarty, S. H.: Notes on Sickle Cell Anemia, J. Lab. & Clin. Med. **12**:536, 1927. (*b*) Diggs and Pettit.[1b] (*c*) Ogden.[1c]

3. Sydenstricker, V. P.: Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12 (July 5) 1924.

4. (*a*) Haldane, J. B. S.: New Paths in Genetics, London, George Allen & Unwin, Ltd., 1941, p. 124. (*b*) Huck, J. G.: Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **34**:335, 1923. (*c*) Snyder, L. H.: Medical Genetics, Durham, N. C., Duke University Press, 1941, pp. 93-96. (*d*) Sydenstricker.[3]

5. Ogden.[1c] Graham and McCarty.[2a]

6. Emmel, V. E.: A Study of the Erythrocyte in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**: 586 (Oct.) 1917.

room temperature. Usually the interval was even shorter. Thus in 2 of the specimens studied practically 100 per cent of the erythrocytes were completely sickled within thirty minutes. This is a rate of sickling at least twenty-four times greater than has been reported previously. It has been stated generally that in similar preparations extensive sickling takes several hours to develop [7] and that it is complete only after twelve to twenty-four hours at room temperature,[8] although the interval may be shortened somewhat by incubation.[9] In moist stasis preparations [10] the blood is first deprived of its oxygen in vivo by application of an arterial tourniquet to the finger for five minutes before the blood is taken. This procedure accelerates sickling,[11] but not to the degree just described.

In the Emmel technic [6] and in others subsequently described [12] a cover slip is placed on the drop of whole blood and the edges are then sealed with a substance which acts as a mechanical barrier to the exchange of gases, such as petrolatum [6] or asphaltum.[1a] All such preparations present objectionable features, which are: (*a*) It is difficult to exclude bubbles of air; (*b*) it usually is not possible to avoid leaks in the peripheral border of the sealing material; (*c*) there is no uniformity as regards the thickness and appearance of the smear, and (*d*) the methods are relatively laborious. All of these difficulties are obviated in the following procedure: A thin film of petrolatum is spread evenly across the whole surface of a no. 1 cover slip with an applicator stick. (The film of petrolatum must be extremely thin and barely visible, if at all, to the naked eye). The drop of fresh blood is then placed on a clean glass slide, and the cover slip is immediately pressed down on it so that a film of blood extends under the whole cover slip and oozes out from under the edges. The edges of the cover slip are then further pressed down with an applicator stick, so that they are firmly sealed to the glass slide, until the color of the blood is no longer visible. By this means an even, thin suspension of cells essentially free of air bubbles can be made with considerable ease. Although the suspension probably averages less than 20 microns in thickness, the cells are free in their own plasma (or whatever other suspension medium is being used) and can be observed individually. In this preparation, the erythrocytes can be made to move in slender streams and rivulets by pressure on the cover slip, and their flexibility may be thereby studied.

A material advantage of this method is that completely sealed preparations can be made almost instantly from fresh blood, and the opportunity for gaseous exchange between the blood and the atmosphere is thus minimized. The preparation for the first few minutes, therefore, may be taken to represent approximately the actual appearance of erythrocytes when circulating within the blood vessels.

A film of liquid petrolatum is inferior to one of petrolatum in the method described, probably because it is a poorer mechanical barrier to diffusing gases.

The process of sickling commences with a concentration of hemoglobin in one part of the cell, usually the periphery, giving it a doughnut appearance. This form of the cell is flexible and easily changes shape when passing between fixed objects in movements of the fluid. During these movements, and also while the cell is stationary, the cytoplasm becomes thinned at one point and eventually ruptures, opening out into a crescent and sometimes having a "ghost" of cell membrane within the arc. As described by Graham and McCarty,[2a] in some cases the hemoglobin appears to be in a state of rapid agitation just prior to the formation of a crescent. We believe, however, that this may be an optical illusion. In such a preparation the percentage of true sickle forms is low in relation to the incidence of other bizarre shapes assumed by the cells. Always there appear long delicate processes and tapering points projecting from the cell. A particular type, the "holly wreath" form of Sherman,[8a] is also seen, and more abundantly in less perfectly sickled specimens. The sickling alteration occurs with varying regularity and occasionally less precipitously than has been described here. The fibrin network which is assumed to be present [6] never seems to impede the freedom of motion of the erythrocyte.

The moment a cell becomes sickled its flexibility is lost and it appears as fixed and rigid as a crystal of ice as it moves about and abuts against cells and fixed objects. This rigidity causes it to stand out in contrast with the unaltered cells, which continue remarkably

7. (*a*) Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695 (Feb. 25) 1939. (*b*) Diggs and Pettit.[1b] (*c*) Emmel.[6]

8. (*a*) Sherman, I. J.: The Sickle Cell Phenomenon with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, Bull. Johns Hopkins Hosp. **67**:309, 1940. (*b*) Graham and McCarty.[2a] (*c*) Huck.[4b]

9. Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia, Am. J. Dis. Child. **26**:132 (Aug.) 1923.

10. Scriver, J. B., and Waugh, T. R.: Studies on a Case of Sickle Cell Anemia, Canad. M. A. J. **23**:375, 1930.

11. Diggs and Pettit.[1b] Scriver and Waugh.[10]

12. Beck and Hertz.[1a] Diggs and Pettit.[1b] Ogden.[1c] Sydenstricker.[3] Huck.[4b] Sherman.[8a] Diggs and Bibb.[7a] Sydenstricker, Mulherin and Houseal.[9]

spongelike, soft and readily flexible, reflecting every movement of the fluid with gentle undulations and changes in shape.

This observation, that sickled cells present a rigid, brittle appearance as contrasted with normal cells, is an interesting corollary to the demonstration by Diggs and Bibb [7a] that sickled cells are considerably more fragile to mechanical trauma than unaltered erythrocytes. It is also important in the elucidation of the pathologic physiology of sickle cell disease, which depends initially on a blockade of the capillaries and smaller blood vessels by abnormally shaped red corpuscles.[13] (In another communication we will present photomicrographs of this phenomenon as seen in a biopsy specimen of muscle.) It acquires additional significance in the recent observations by Dameshek and his co-workers and by Ham and Castle that erythrostasis and cell trauma promote hemolysis of the red cells.[14]

2. EFFECT OF SUSPENSION MEDIUMS ON SICKLING

The patient's whole blood was defibrinated and separated into cells and serum, the cells being washed in 0.85 per cent isotonic solution of sodium chloride. A sample of normal blood of a different blood group was treated in the same way, and parallel controls set up.

No abnormality of the normal blood cells appeared in any of the samples. The blood cells obtained from the patient with sickle cell disease assumed the abnormal shape equally well in homologous serum, foreign serum and saline solutions, but slowly and incompletely, there being approximately 80 to 90 per cent of sickled forms in fourteen to twenty-four hours. In saline solution suspensions the sickling was highly variable. This was probably due to the varying concentrations of washed cells suspended in the saline solutions. It was observed that a higher concentration of cells in a suspension facilitated the sickling process. Under such conditions the available oxygen was consumed more readily, this creating the circumstance which promotes sickling. It was further evidenced by progressively increasing the dilution of washed cells. Sickling diminished and eventually ceased entirely, presumably because too much oxygen remained in solution to be consumed in the metabolism of the remaining cells.

The sickling in saline solution, which has been observed repeatedly,[15] establishes that it is a characteristic inherent in the susceptible erythrocyte itself. In this connection we desire to note the fact that we later studied sickling in a suspension of red blood cells washed three times and suspended in solution of potassium chloride (1.083 Gm. per hundred cubic centimeters). This work was occasioned by the belief that the behavior of the potassium ion was closely associated with sickling.[16] It was found that sickling progressed at the same rate and to the same extent (almost 100 per cent in twelve hours) in the potassium chloride as in the sodium chloride solutions.

Sickling was more pronounced in unaltered whole fresh blood than in either serum or saline solution. This observation suggested that the phenomenon might be encouraged by factors present in whole blood (coagulated in the sealed preparation) and absent in serum. Chief of these is fibrin, for thrombin and free thromboplastin are probably well represented in freshly prepared serum. Plasma, on the other hand, differs from serum chiefly by the presence of fibrinogen and the absence of thrombin and free thromboplastin. Preparations of oxalated whole blood (suspension medium, plasma) required ten hours for complete sickling. This decidedly is slower than with unaltered whole blood, which naturally forms a coagulum. However, sickling was more rapid and more complete than with cells suspended in serum (homologous or foreign), although the difference was not great enough to be conclusive. The addition of thrombin or of calcium and thromboplastin to the various suspensions of red blood cells induced no detectable effect on the extent or rate of sickling.

It appears, therefore, that there is a great difference in the rate and extent of sickling between whole fresh blood and mediums in which there is no fibrin meshwork. To determine this relationship further, sickling was studied in a sealed preparation immediately after defibrination. The specimen showed sickling to be much less pronounced than in preparations of unaltered fresh blood.

13. Diggs and Pettit,[1b] Sherman,[8a] Diggs, L. W., and Ching, R. A.: Pathology of Sickle Cell Anemia, South. M. J. **27**:839, 1934. Diggs, L. W.; Pulliam, H. N., and King, J. C.: The Bone Changes in Sickle Cell Anemia, ibid. **30**:249, 1937. Bridgers, W. H.: Cerebral Vascular Disease Accompanying Sickle Cell Anemia, Am. J. Path. **15**:353, 1939.

14. (*a*) Dameshek, W., and Miller, E. B.: Pathogenetic Mechanisms in Hemolytic Anemias, Arch. Int. Med. **72**:1 (July) 1943. (*b*) Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127, 1940.

15. (*a*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy; Experimental Study of Sickle Cell Formation, Arch. Int. Med. **39**:233 (Feb.) 1927. (*b*) Huck,[4b] (*c*) Diggs and Bibb.[7a]

16. The potassium value of the erythrocytes had been found to be significantly less than normal. These figures are given later in this paper.

These findings add strong support to the frequently challenged[17] hypothesis of Graham and McCarty that sickling is in some way related to the development of the fibrin net.[2a]

In an attempt to study this factor further, experiments were designed in which whole blood was heparinized and a solution of pure thrombin added quickly to it immediately before a sealed preparation was made. These experiments failed, because the fibrin clot formed so completely and so quickly on the addition of thrombin that the experiment could not be set up in time.

3. RELATION OF OXYGEN TO THE PHENOMENON OF SICKLING

Sickle cells return immediately to a normal biconcave shape on exposure to oxygen.[18] This phenomenon was readily demonstrated in our preparations both on whole blood and of cells suspended in the various mediums used. The study was executed in the following manner: The cover slip was pried away from the slide onto which it was sealed, so that the cells were exposed to air. Immediately it was returned to the slide, which resealed the preparation and excluded almost all of the air. Whereas about 100 per cent of the erythrocytes were sickled before this operation, almost all of them showed their normal biconcave (or sometimes crenated) shape as soon as they were again brought into focus. The preparations made by our method had thicknesses which approximated the diameter of a red blood cell; hence exposure to air of this thin film for only one or two seconds was sufficient to oxygenate the hemoglobin so that the cells resumed their normal shape. When the preparation was allowed to stand a few hours after this experiment sickling reappeared.

To follow more directly the return to normal shape of the red cells, this procedure was followed: A no. 1 cover slip was marked across its center with a diamond pencil, and then a sealed preparation was made with it. A magnification of 500 diameters was used, and the cover slip was broken beneath it. The edges were then teased apart while the examiner was directly watching the specimen. The sickle cells were seen flowing across the air boundary, and as soon as they moved from the suspension to the air their shape appeared normal. Because of differences in refraction the boundary between the air and the fluid could not immediately be brought into focus, so that the actual rounding up of the sickled cells could not be followed.

The relation of oxygen to the phenomenon of sickling was first investigated and clarified by Hahn and Gillespie in 1927.[15a] By passing washed gases through a hanging drop of blood from a patient with sickle cell anemia they observed that when the cells were in contact with oxygen in adequate concentration the normal biconcave shape appeared to be stable to all alterable factors, such as p_H and variations of osmotic pressure. When the oxygen was removed from the blood or reduced to a tension below 45 mm. of mercury, the sickled form appeared to be entirely stable. The cells containing oxygenated hemoglobin did not sickle, but when the hemoglobin was converted into the reduced form the cells invariably sickled. Substituting carbon monoxide for oxygen, they determined also that cells containing carboxyhemoglobin would not sickle, but again when the hemoglobin was converted to the reduced form the cells inevitably sickled. They thus established the fact that sickling depends on the state of hemoglobin in the red cells. When the hemoglobin is in the reduced form the abnormal shape of the erythrocyte is stable; when it exists in the combined form the normal shape is stable. Other factors, such as p_H, had no effect on sickling except as they influenced the state of the combination of hemoglobin.

4. EFFECT OF ELECTROLYTE IONS ON SICKLING

The state of combination of hemoglobin is not in itself a simple phenomenon.[19] When the hemoglobin of a cell loses its oxygen (or any other gas in combination with it) there are complex alterations of electrolyte ions. Combined hemoglobin (oxyhemoglobin) is a stronger acid than reduced hemoglobin. When oxygen is released from combination, base must also be dissociated from the hemoglobin salt for the medium to remain at a constant p_H. A considerable fraction of the potassium hemoglobinate is thus dissociated with the dissociation of oxyhemoglobin. The concentration of osmotically active potassium ions in solution in the cell is thus suddenly increased. This base is buffered by combining with the bicarbonate ion derived from carbonic acid. The concentration of the bicarbonate ion within the cell is thus increased. In order to restore the equilibrium according to Donnan's law, this additional bicarbonate must diffuse out of the cell to restore the balance of bicarbonate ions on either side of the cell membrane. The bicarbonate ion thus lost to the red

17. Huck.[4b] Sherman.[8a]

18. Klinefelter, H. F.: The Heart in Sickle Cell Anemia, Am. J. M. Sc. **203**:34, 1942. Sherman.[8a] Diggs and Bibb.[7a] Hahn and Gillespie.[15a]

19. The data on the chemistry of the red blood cell are taken from Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, chaps. 18 and 19.

cell is replaced by an equivalent amount of chloride iron, in the process known as "chloride shift." In addition to these ionic changes the total concentration of osmotically active ions in the red cell is necessarily increased considerably by the release of potassium and the neutralization of that base by bicarbonate ion. Therefore the water content of the cell increases with a restoration of osmotic equilibrium. The cell containing hemoglobin in reduced form is thus larger in volume than the cell containing the hemoglobin in combined form (at physiologic hydrogen ion concentrations).

Investigation was undertaken to determine whether or not these ionic changes themselves were the factors immediately responsible for sickling. Two possibilities suggested themselves: (1) that sickling might be associated with quantitative variations from the normal in the bicarbonate and chloride shifts and/or (2) that it was related to variations in the proportion of ionized intracellular potassium.

In the first experiment an attempt was made to measure the extent of the chloride shift of the red blood cells. Determinations were made by quantitative analysis of serum chloride ion according to the method of Schales and Schales.[20] The differences between the chloride shift of the patient's blood and that of the normal control blood were found not to be measurable by this procedure; hence this line of investigation was abandoned.

Dissociation of combined hemoglobin, the exciting factor in sickling, presents two variables, as noted. These are: the dissociation of the hemoglobin per se and the ionic changes which accompany this dissociation. A second experiment was designed to maintain the hemoglobin in a constant state while the ionic balance was varied widely. The relation of the ionic changes to sickling was thereby studied independently of the condition of the hemoglobin.

Hemoglobin becomes saturated with carbon monoxide at a tension of 25 mm. of mercury.[21] A concentration of 5 per cent carbon monoxide when equilibrated with blood, therefore, should leave none of the hemoglobin in the reduced form under any conditions. If the p_H of the blood could then be reduced to or below the isoelectric point of carboxyhemoglobin, more of the potassium would thereby be released from its hemoglobin salt than occurs in the normal respiratory cycle. The resulting electrolyte changes would be identical with those occurring in the respiratory cycle. It is essential that the alterations in p_H be not accomplished by adding inorganic acid to the blood, as was done in the investigations of Hahn and Gillespie,[15a] because such an addition distorts the ionic balance between serum and cells and thereby alters the changes that have been described, which occur in conformance with Donnan's law. These changes, however, would not be disturbed by a total increase in bicarbonate ion, which readily adjusts itself according to the Donnan equilibrium between serum and cells. Such a total increase would in no way alter the bicarbonate and corresponding chloride shifts occasioned by the release of potassium from its hemoglobin salt. A high concentration of carbon dioxide equilibrated with the blood, therefore, is the obvious means through which the desired reduction in p_H can be accomplished.

Blood equilibrated with 95 per cent carbon dioxide has a p_H of 6.2 as determined by the Henderson-Hasselbach equation. This value is considerably below the isoelectric point of carboxyhemoglobin, which is 6.65.[22] At a p_H of 6.2 all of the potassium carboxyhemoglobinate is dissociated. The potassium ion is therefore entirely in osmotically active form, and the bicarbonate and chloride shifts, as well as the resulting hydration of the red cells, all occur to an exaggerated degree. If sickling fails to occur in such a preparation it would indicate that the electrolyte changes described are not the means per se responsible for the phenomenon of sickling. The following study demonstrated this to be the case.

Heparinized whole blood was equilibrated with a mixture of 5 per cent carbon monoxide and 95 per cent carbon dioxide. The carbon monoxide gas was generated by adding anhydrous formic acid to hot sulfuric acid.[23] This gas was washed in solution of calcium hydroxide to remove any volatile acids present, and then passed through distilled water containing 3 or 4 drops of phenolphthalein solution. Color did not develop in the indicator bottle; hence the gas, which had been washed free of acid, was considered to be strictly neutral in reaction. The carbon dioxide gas was taken directly from a tank into clean washed rubber balloons and was passed once through distilled water. Then 950 cc. of carbon dioxide and 50 cc. of carbon monoxide were measured directly into a graduate by water displacement. The mouth of the graduate was sealed under water with a two hole rubber stopper from which projected two leads of rubber tubing, each lead being filled with water and clamped. The gases were mixed by shaking the

20. Schales, O., and Schales, S. S.: A Simple and Accurate Method of the Determination of Chlorides in Biological Fluids, J. Biol. Chem. **140**:879, 1941.

21. Peters and Van Slyke,[19] vol. 1, p. 342.

22. Peters and Van Slyke,[19] vol. 1, p. 538.

23. Peters and Van Slyke,[19] vol. 1, p. 342.

approximately 200 cc. of water which remained in the graduate. Two cubic centimeters of the patient's whole heparinized blood was equilibrated for twenty minutes in a separatory funnel with this mixture of carbon dioxide and carbon monoxide gases, during which process the vessel was flushed four times with the gas mixture.

Under anaerobic conditions a sample of this blood was then transferred under oil to a solution of 0.85 per cent sodium chloride in 4 per cent neutral solution of formaldehyde, made up according to the method of Beck and Hertz.[1a] After fixation for four or five minutes smears were prepared from the suspension. No sickle cells could be found. A wet preparation was made from the equilibrated blood according to the method that has been described. No sickle cells could be seen on immediate examination of the blood, and the cells remained entirely normal in appearance over a six day period of daily observation.

As a control for this experiment the same sample of blood, still in the separatory funnel, was then equilibrated with 100 per cent carbon dioxide. Immediate sickling was demonstrated in more than 90 per cent of the cells in both a sealed preparation and a fixed specimen. The sample was then equilibrated with pure oxygen, and similar wet and fixed specimens were prepared. Sickling was not demonstrable in the two preparations, but when next observed, about twenty-four hours later, the wet smear revealed sickling in practically every cell. It should be noted incidentally that we found the saline-formaldehyde solution method of fixation not entirely satisfactory. If the cells were fixed for less than about four minutes the fixation was imperfect, and if the mixture was left for longer than five minutes it turned brown and the cells fragmented.

These observations demonstrate that sickling appears to be unrelated to the variations in ionic balance that have been described. We found, however, that the potassium content of the erythrocytes may be significantly less than normal. Thus, after the patient had recovered from a crisis and was asymptomatic the potassium content of the plasma was 19.1 mg. per hundred cubic centimeters and the red cell content was 302 mg. Two weeks later, about eighteen hours after the onset of a severe crisis, the plasma potassium was reduced to 13.8 mg. per hundred cubic centimeters and the red cell content rose to 346.3 mg. but was still appreciably less than normal. No explanation is offered at this time except to note the possible implication that the level of available potassium in the cell might play a role in the mechanism of sickling.

COMMENT

The observations described when correlated with those of Hahn and Gillespie afford almost unequivocal evidence that the dissociation of combined hemoglobin bears a causal relationship to the phenomenon of sickling. Of note in this connection is the observation by Sherman [8a] that sickled cells are birefringent when observed through the polarizing microscope. The characteristic disappears when the cells resume the normal form. Although a clear interpretation of this phenomenon cannot be offered at the present time, it suggests that certain molecules of the cell become reorientated when the cell undergoes sickling. Obviously such refractile alteration is determined by changes other than those of ionic electrolytes alone.

The evidence cannot be absolutely conclusive, however, until all other possible explanations for the fact that sickling and the dissociation of oxyhemoglobin are simultaneous occurrences can be ruled out. They may be simply parallel incidents, both the result of a single phenomenon but not related causally to each other. It is conceivable, for instance, that sickling may result from even a slight abnormality in the metabolism or the respiratory function of the erythrocyte. Thus, at the time the available oxygen in the preparation is consumed the altered respiratory metabolism of the red cell may reach a stage in which the sickle form is stable. This possibility could be studied by inactivating the metabolic processes within the cell with cyanide and then artificially combining and dissociating the hemoglobin by one of the methods that has been described. If sickling occurred it would demonstrate that the phenomenon did not depend on the metabolism of the red cell, which would have been reduced to a cipher by the cyanide, while the interchange of gases in the hemoglobin remained unaffected.

Several factors make it appear improbable that sickling is precipitated by a complex metabolic rather than a simple chemical change. There is evidence from our own (unpublished) observations as well as from the observations of others [7a] that sickling is rarely seen in the younger forms of erythrocytes, such as reticulocytes and normoblasts. If the metabolism of the red cell were intimately associated with sickling one would expect these young forms to sickle par excellence. Likewise the phenomenon should tend to disappear as the cell grows older and approaches the ametabolic "perfect machine" toward which it is known to progress. Furthermore, the invariable association of sickling simultaneous with the oxygen asphyxia of the cell argues for a causal relationship between the two occurrences.

Lastly, the instant restoration of the sickled erythrocyte to discoid form on exposure to oxygen would be difficult to explain by the inherent metabolism of the red blood cell alone. Nevertheless an experiment designed to investigate the metabolism of this type of erythrocyte should be performed before the possible role of that factor in sickling can be definitely eliminated.

Another line of investigation which requires further study is a quantitative one to determine the relation between the amount of dissociated and that of combined hemoglobin present at the time of sickling. The fact that cells sickle in vivo and in fresh blood indicates that only a certain percentage of the hemoglobin must be in the uncombined form for the phenomenon to take place. An oxygen tension of 45 mm. of mercury or lower has been found necessary to produce sickling.[15a] Actually, the necessary oxygen tension (which may be taken as an index of the ratio of combined to dissociated hemoglobin) varies in different patients and in different cells of the same patient. This is self evident by the fact that in various preparations some cells are sickled and others are not and that as the oxygen tension is reduced an increasing number of cells sickle until all of the cells are abnormal. Assuming that the degree of hemoglobin dissociation is a direct function of oxygen tension, some cells sickle when a small part of their hemoglobin is uncombined, while sickling in others requires dissociation of almost all of the oxyhemoglobin. All variations of sickling thresholds exist between these two extremes. It has been shown in our studies that none of the cells will sickle if all of the hemoglobin is in combined form and that all of them are susceptible if the presence of combined hemoglobin is reduced to a sufficient minimum.

The difference in the ratio of combined to dissociated hemoglobin required for sickling is well illustrated by a study of blood samples from different patients. The father of our patient was found to have the symptomless sickle cell trait. A wet smear of his blood showed sickling in only about 50 per cent of the cells after eighteen hours, a rate markedly below that of his son. Our interpretation of this slow rate is that after eighteen hours the oxygen tension was still not reduced below the sickling threshold of about one half of the cells in the preparation.

The difference in sickling threshold may be used as the basis of a differentially diagnostic test between the sickle cell trait and the sickle cell disease. Sherman [8a] found by the anaerobic fixation method [1a] that the venous blood of patients with sickle cell disease always contained a large number (30 to 60 per cent) of sickle cells, and that the same method revealed only rare sickle cells in the blood of persons with the trait alone. This investigator also determined that sickling depended directly on the oxygen tension. He showed, further, that the blood cells from a patient with the sickle cell disease showed progressive sickling as the oxygen tension was reduced by evacuation and that the erythrocytes from a person with the sickle cell trait, on the other hand, showed no sickling until the oxygen tension was reduced to 18 mm. of mercury.

Variations in the sickling threshold, as determined by the oxygen tension or the degree of dissociation of hemoglobin, may be significant in explaining the genesis of the crises of the sickle cell disease. There is evidence, as previously noted, suggesting that the susceptible erythrocytes tend more to sickle as they grow older, or at least that the immature forms show a relatively diminished tendency to sickle. In another communication evidence will be offered to support the theory that the crises are precipitated by an increasing accumulation of sickled cells, that is, of cells in which the sickled form is stable in the oxygen tension of arterial or capillary blood. We believe that these cells are at least as viable as normal red blood cells and that the extensive phagocytosis of these cells [24] is actually only of particles of sickled cells which have become fragmented by the trauma of capillary passage. Our observation, already described, that the moment a cell in vitro acquires the sickled form its flexibility is abruptly lost and that it appears as rigid as a crystal of ice as it moves about and abuts against cells and fixed objects is pertinent to the immediate problem of the hemolytic crises. It is compatible with the findings of Dameshek and his co-workers [14a] and of Ham and Castle,[14b] who have demonstrated (in addition to other factors) the important roles played by trauma and stasis of the erythrocytes in hemolytic processes.

The evidence indicates that the difference in sickling threshold may depend on differences in age of the cells. A sickle cell crisis in that event would be identified with the accumulation of aging cells. If the number of circulating abnormal cells became too great they might suddenly precipitate out of the blood stream in a massive "capillary blockade." This hypothesis has received confirmation in our observation that a progressive rise in the number of sickle cells in the circulating blood precedes the crisis. The blood rejuvenated (as reflected by increased reticulocyte and normoblast counts) by a crisis contains relatively few sickled cells, and this number increases until another crisis is precipitated. The

24. Huck,[4b] Sydenstricker, Mulherin and Houseal.[9]

increased osmotic resistance of sickled cells [25] and their proved viability for at least twenty-three days when transfused into foreign blood [3] afford support to the hypothesis that their resistance to other than mechanical trauma in the circulating blood is not decreased. The mechanism which sets off the sudden capillary blockade appears also to be related to alterations in the process of coagulation of blood and will be discussed in a later report on the clinical aspects of the sickle cell disease.

SUMMARY

Specimens of blood of a patient with severe sickle cell disease were studied by a modification of the sealed smear technic for demonstration of sickling.

Sickling is a property inherent in the susceptible erythrocyte. It appears to be encouraged by coagulation of the blood specimen. Erythrocytes sickle at various specific thresholds as determined by the ratio of dissociated to combined hemoglobin. There is evidence to indicate that as the cells age the sickling threshold becomes lower.

Sickling appears to be unrelated to variations in electrolyte ionic balance. The level of available potassium in the cell may play a significant role in the sickling phenomenon.

Two proposals are made for further investigation. One line of study should analyze the relationship of the red cell metabolism to the sickling phenomenon. The other involves quantitative studies of the sickling threshold as determined by oxygen tension.

NOTE.—A single preliminary test reveals that with radioactive potassium the red blood cells from the patient reported on were about twice as permeable to potassium ion as were his normal (control) sister's erythrocytes. It appears to us that this observation, if confirmed, will prove to be of the utmost importance.

Dr. William H. Summerson, of Cornell University Medical College, gave invaluable aid in the experiments described. Dr. Ade T. Milhorat, of New York Hospital, Dr. Louis P. Dotti, of St. Luke's Hospital, and Dr. Victor Ross, of Columbia University, College of Physicians and Surgeons, gave assistance and advice. The potassium determinations were made by Dr. Raymond L. Zwemer, of Columbia University, College of Physicians and Surgeons.

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25. Diggs and Bibb,[7a] Hahn and Gillespie.[15a]

BLOOD

A REVIEW OF THE RECENT LITERATURE

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The review on hematology for 1943 has been compiled with considerable difficulty, on account of the many demands on the members of the staff of the Simpson Memorial Institute, and the inaccessibility of some medical journals. It is our hope, however, that we have not omitted any of the important articles which have appeared during the year and that this review is as comprehensive as the preceding ones. If there have been significant omissions, it has been due to an oversight or to the fact that certain journals could not be obtained.

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Changes in the Blood Associated with Infection and Nephritis

Changes in the Blood Associated with Chemical Intoxication

Methods and Miscellaneous Material

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PERNICIOUS ANEMIA

Several important points concerning pernicious anemia have been considered in the literature of 1943. One of the most significant papers is that of Cox,[1] in which he confirms the finding that the anatomic change in the stomach in patients with pernicious anemia is an atrophy of the glands of the fundus, rather than of the pylorus, as previous investigations had suggested. There is an increasing amount of evidence to

1. Cox, A. J.: Stomach in Pernicious Anemia, Am. J. Path. **19**:491, 1943.

indicate that cancer of the stomach is more likely to occur in patients with pernicious anemia than in the population at large in the same age groups. Continued clinical observations indicate the important relationship between the stomach and the formation of blood. Of special interest are the observations relating to the liver and hemopoiesis. During the year it has been shown that removal of the liver anlage from the Amblystoma embryo results in anemia when the embryonic stage is passed and that this anemia may be averted by grafting liver tissue to the tail of the animal. This work has been interpreted as indicating that the liver may not only store the erythrocyte-maturing factor, but also produce a modification of it that is essential to its utilization. No new methods of treatment are advocated, but the increasingly important subject of allergy in relation to the injection of liver extract is considered in a number of papers, and the methods of coping with this complication are discussed. Several articles have appeared dealing with the relationship between pellagra, sprue and pernicious anemia.

Etiology.—It has long been known that pernicious anemia is most common in aged persons. This may be demonstrated by charting the numbers of patients in various decades of life in any given large group of patients against the total numbers of persons living in those age groups. This information is emphasized in a unique way by Kirk and Geert-Jørgensen,[2] who studied the blood of 2,079 persons between the ages of 60 and 96 years, inmates of homes for the aged in Denmark. They found 19 persons with pernicious anemia in this group, which is approximately 1 per cent of the total number examined. According to them, there are about 275,000 persons in Denmark over 65 years of age. This implies that approximately 2,000 persons suffering from pernicious anemia will be found in this age group and thus emphasizes the social importance of the disease.

It is emphasized by Schwartz and Gore[3] that pernicious anemia is more frequent in Negroes than previous reports would indicate. In support of this they report an incidence of 93 cases of the disease in Negroes in a total of 1,000 cases reviewed from the records of the Cook County Hospital in Chicago. Between the years 1931 and 1942, of 426,500 white patients 637 had pernicious anemia, which gives a rate of about 150 per hundred thousand. Of 306,000 Negroes 31 had pernicious anemia, which is a rate of about 10 per hundred thousand. In this series of patients the occurrence of the disease in Negroes was about three and a half times as frequent as would be expected from previously reported figures. They found a somewhat higher incidence in Negro males than in Negro females and a tendency for the disease to develop in younger persons. Their patients were almost all North American Negroes. It is stressed that previous writers have found that Negro patients with pernicious anemia had an admixture of Caucasian blood. According to these observers, this in no way invalidates their observations, since for practical purposes it is not possible in most instances to ascertain with any degree of certainty the presence or degree of admixture. With few exceptions, their patients had the dark skin and eyes, kinky hair and negroid facies characteristic of the full-blooded Negro. They state, however, that these appearances do not exclude even a 50 per cent admixture of white blood. It is their conclusion that even if contrary observations were reported from Negroes native in their lands they would in no way vitiate their findings, since the adaptation of these people to a new mode of living has made them comparable to the Caucasians. Furthermore, they contend that, since the North American Negro is a hybrid group, from a practical standpoint, the question is an academic one.

Role of Changes in the Gastrointestinal Tract: As Fox and Castle had recently produced evidence, contrary to previous reports, suggesting that the site of the production of the "intrinsic factor" is the fundus and body of the stomach, Cox[1] considered it pertinent to reconsider the gastric changes in patients with pernicious anemia. His findings are based on examination of the stomachs of 6 patients who died of pernicious anemia, of the stomach of a patient with sprue and of 175 stomachs from routine necropsies. The outstanding feature in the stomachs of patients with pernicious anemia was the marked alteration in the mucosa of the fundus and the body in contrast to the relative freedom from abnormalities in the pyloric region. This has previously beeen emphasized by Meulengracht. The changes in the fundic zone were extensive and severe. The mucosa was only about one-half the thickness of that in the pyloric zone. This abnormal thinness was due to a pathologic type of mucosa, the most important alteration of which was the absence of the chief and parietal cells. The loss of the specific cells in this area was complete in all except 1 case, in which a few small groups of atypical glands

2. Kirk, E., and Geert-Jørgensen, H.: Frequency of Pernicious Anemia in the Aged, Acta med. Scandinav., 1941, supp. 123, p. 213.

3. Schwartz, S. O., and Gore, M.: Pernicious Anemia in Negroes, Arch. Int. Med. **72**:782 (Dec.) 1943.

containing occasional cells resembling the parietal variety were present in the sections taken from the upper portion of the lesser curvature. No chief cells or parietal cells were found in other portions of the stomach. The changes in the pyloric zone were inconstant and considered to be insignificant. There did not appear to be any relation between the appearance of the stomach and the duration of the disease or the amount of treatment which had been given. The stomach removed three hours after death from a patient with tropical sprue showed none of the changes which characterized the stomachs of the patients with pernicious anemia. The gastric lesions in the patients with pernicious anemia were different from those accompanying other diseases. Hence it is suggested that they may represent a specific change, perhaps the result of massive destruction of the highly differentiated parietal and chief cells with only slight if any injury to the less highly differentiated cells. If such damage were followed by limited repair, associated with the mild lymphoid infiltration. changes like those observed in the stomachs of patients with pernicious anemia might be produced. According to the author, such damage might appear only in unusually susceptible persons, in the same way that necrosis in the liver is observed only occasionally after administration of cinchophen or that injury to the bone marrow develops after chemotherapy only in a few presumably susceptible persons.

It is reported by Farris, Ransom and Coller [4] that of 49 persons on whom total gastrectomy was done at the University Hospital of the University of Michigan 4 survived the operation for longer than two years. Careful examinations of the blood failed to show evidence of macrocytic anemia in these patients, although it was noted that after the operation many of the patients did have anemia of the hypochromic, microcytic type. In our opinion it is easy to understand why macrocytic anemia does not develop when there is a partial resection of the pyloric end of the stomach. Removal of the entire stomach, however, presents quite a different situation. Theoretically, on the basis of our present knowledge, if the intrinsic factor is secreted by the cells of the fundus of the stomach their elimination by a total gastrectomy should result in the development of macrocytic anemia in every case. It should be kept in mind, however, that many patients do not survive for a sufficient period of time to permit pernicious anemia to develop and, furthermore, it is possible that the intrinsic factor may be formed elsewhere in the gastrointestinal tract. In any event, knowledge relating to this subject is still incomplete, and the correct answer concerning the precise and complete relationship of the gastrointestinal tract to pernicious anemia awaits further investigation.

Rhodes and Grunberg [5] state that only about a score of well authenticated cases of anemia of the hyperchromic, macrocytic type resulting from partial gastrectomy have been recorded. They add the report of an additional case, in which the patient responded to liver therapy. The patient was a woman aged 61 who had been operated on thirty years before for a perforated gastric ulcer. Fifteen years after that operation a partial gastrectomy was performed, at which time three quarters of the stomach was removed. A few months before the examination which forms the basis of this report, pallor and edema of the ankles developed. The blood showed a typical macrocytic anemia with a high color index. The red blood cell count was 1,400,000 per cubic millimeter, the hemoglobin content 33 per cent and the mean corpuscular volume 116 cubic microns. A sternal puncture disclosed a typical megaloblastic marrow. Since it has been demonstrated that the intrinsic factor is secreted by the glands in the fundic end of the stomach, it is difficult to conceive how by a resection of three fourths of the lower end of the stomach a sufficient amount of glandular tissue could be removed to cause a deficiency of this factor.

Sailer [6] reports an unusual case of diffuse metaplastic gastritis in a patient with prolonged cachexia and macrocytic anemia. The patient was a Negro woman aged 52 who had had recurrent attacks of vomiting for six years, abdominal pain and progressive general weakness. There was advanced cachexia associated with macrocytic anemia with a high color index. The lowest red blood cell count recorded was 1,500,000 per cubic millimeter, with 5 Gm. of hemoglobin per hundred cubic centimeters. There was no response to liver therapy. At necropsy the stomach was found to be uniformly reduced in size and its wall to be regularly thickened and showing diffuse squamous metaplasia of the mucosa. No apparent cause of the gastric changes was found, but the author states that the possibility of vitamin A deficiency must be considered.

4. Farris, J. M.; Ransom, H. K., and Coller, F. A.: Total Gastrectomy: Effects upon Nutrition and Hematopoiesis, Surgery **13**:823, 1943.

5. Rhodes, A. J., and Grunberg, A.: Macrocytic Anaemia Following Partial Gastrectomy, Brit. M. J. **1**:726, 1943.

6. Sailer, S.: Diffuse Metaplastic Gastritis in Patient with Prolonged Cachexia and Macrocytic Anemia, Arch. Path. **35**:730 (May) 1943.

The most uncommon association of carcinoma and tuberculosis of the stomach in a patient with pernicious anemia was observed by White.[7] This patient, a man aged 64 when observed by White in May 1942, had begun to show the symptoms of pernicious anemia in 1922, at the age of 42. Four years later, in 1926, he began taking liver, and as a result all of his symptoms were controlled. Fifteen years after the liver therapy was begun, in 1941, he first complained of mild bloating, anorexia and loss of 15 pounds (6.75 Kg.) of body weight in six months. Achlorhydria was present. The blood showed no changes from normal, doubtless because of the beneficial effect of liver therapy. Operation revealed an adenocarcinoma of the stomach (of grade 4, or the maximal degree of malignancy) and the typical changes of tuberculosis. It was not possible, however, to demonstrate tubercle bacilli either by inoculation of guinea pigs or by microscopic search of the tissue removed. The relationship of carcinoma of the stomach and tuberculosis is discussed, and a review of the literature is given. According to White, in the several hundred cases of tuberculosis of the stomach it has been found that carcinoma has also been present in 10 per cent. The evidence is reviewed which indicates that the incidence of gastric carcinoma in patients with pernicious anemia is on the increase. The etiologic significance of gastritis to carcinoma is discussed.

Evidence is at hand, according to Rigler,[8] which indicates that the same type of gastric mucous membrane is conducive to both pernicious anemia and carcinoma of the stomach. Whether the abnormality is due to chronic gastritis or to secondary atrophy, or to primary atrophy on a familial basis, has not yet been determined. The author emphasizes that reports of carcinoma of the stomach developing in patients with pernicious anemia have had a sharp increase in the past decade. This is in part due to an increased number of roentgen ray examinations and to the fact that patients with pernicious anemia now live for a longer period as a result of more effective anti-pernicious-anemia therapy. The exact incidence of carcinoma of the stomach in living persons is not known, but a reasonable estimate, according to Rigler, is that the condition occurs in about 3 persons per thousand of all those living over the age of 45 years. In patients with pernicious anemia, there is evidence to indicate that carcinoma of the stomach occurs with a much greater frequency. Rigler reports that since 1939 he has reexamined all patients with pernicious anemia by means of roentgen rays for evidence of carcinoma of the stomach at six month intervals. His preliminary studies suggest that gastric carcinoma is far more common, perhaps ten times as common, in patients with pernicious anemia than in the rest of the population. Furthermore, it is evident from his studies that benign epithelial tumors are likewise far more frequent in such patients. He has also observed polyps, apparently benign, both roentgenologically and gastroscopically, develop into obvious carcinoma after refusal of the patients to have the tumors extirpated. He concluded that the number of patients without symptoms or signs related to the stomach who exhibit fairly obvious tumors is startling and that this more than confirms the impression that carcinoma of the stomach is extremely insidious in its onset. From the data which he has collected, he recommends that every patient with pernicious anemia have a roentgen examination of the stomach every six months. He concludes with the statement that when one considers the increased life expectancy of patients with pernicious anemia due to modern treatment, the surgical treatment of early cancer or of a benign polyp which may likely develop into a cancer, is thoroughly worth while.

In an attempt to discover a basis for the commonly associated gastric complaints in patients with pernicious anemia, Jacobson and Palmer[9] have studied the relationship between the anemia, the gastric emptying and the gastrointestinal symptoms in a group of patients with this disease and with other severe types of anemia. Patients with pernicious anemia in relapse, the same patients after a return of the red blood cell count to normal with therapy and a group of persons with pernicious anemia who had been under control for months to years were utilized for study. It was observed, with 1 exception, that when the red blood cell count was below 1,500,000 per cubic millimeter there was a significant prolongation of emptying time of the stomach as determined by means of roentgen studies after a barium sulfate meal and by fluoroscopic examination. This was observed not only in patients with pernicious anemia but in persons with other forms of severe anemia. The majority of patients with extreme anemia of any type had mild to severe abdominal complaints

7. White, R. R.: Simultaneous Carcinoma and Tuberculosis of the Stomach in a Case of Pernicious Anemia, Proc. Staff Meet., Mayo Clin. **18**:165, 1943.

8. Rigler, L. G.: Pernicious Anemia and the Early Diagnosis of Carcinoma of the Stomach, Radiology **41**: 187, 1943.

9. Jacobson, L. O., and Palmer, W. L.: The Effect of Anemia on Gastric Emptying, Gastroenterology **1**: 1133, 1943.

which in general disappeared promptly and completely when the gastric emptying time returned to normal after adequate specific or palliative therapy. Contrary to the general belief that the gastrointestinal motility is increased and the passage of material from the stomach and through the intestinal tract is accelerated in pernicious anemia, evidence is presented which indicates that these functions are either normal or delayed in patients with severe anemia. It was also apparent from these studies that achlorhydria per se does not significantly affect the rate of gastric emptying.

Role of the Liver in Hemopoiesis: Unique and important experiments have been performed by Copenhaver [10] which have a bearing on the relation of the liver to the formation of blood in Amblystoma embryos. The results are of interest when compared with the modern views concerning the causation of pernicious anemia in man. This observer removed the liver anlage from Amblystoma embryos but found that this did not produce an important change in the blood during the embryonic stage. On the other hand, pronounced symptoms, including anemia, always appeared when the animals were kept for a sufficient time beyond the embryonic stage. The conclusion was that the major factor in producing anemia after embryonic hepatectomy is the absence either of some substance which is stored in the liver or of some metabolic process controlled by the liver and essential for erythropoiesis in other hemopoietic organs. When the liver tissue was present as a graft in the tail of the animal, a position which prevented any connection with the digestive tract, the erythrocytes continued to multiply in the spleen and in the general circulation. It is assumed by the author that if the graft had prevented any anemia merely by acting as a storage depot for a substance similar to the erythrocyte-maturing factor in man, liver extracts should have been effective in treating the anemia of liverless animals. The results of injecting and feeding potent liver extracts have so far been negative. It is suggested by the author that the liver may not only store the erythrocyte-maturing factor but also produce a modification of it that is essential to its utilization. This view is in accord with the one expressed by Robscheit-Robbins and Whipple in 1925, when they concluded from their studies on dogs that the liver's part in erythropoiesis is not limited to the storage of an erythrocyte-maturing factor and that in addition this organ plays an important part in the production of some substance essential for development of red blood cells.

An article by Colvin [11] again raises the question of the relation of the liver to the "hyperchromic" anemias. This relationship is of interest because: (1) previous observers, such as Bethell and Harrington, have reported that 22 per cent of the patients with true pernicious anemia have associated disease of the biliary tract; (2) it is known that when extensive changes occur in the liver, such as cirrhosis, a macrocytic anemia resembling pernicious anemia may appear, and (3) it was previously suggested by Jones and Joyce that bacteria infecting the gallbladder might be one cause for the hemolysis which was then thought to be the chief cause of pernicious anemia. In a study of 20 patients whom Colvin states presented the syndrome of chronic cholecystitis without stone, there was anemia with an erythrocyte count rarely below 3,000,000 per cubic millimeter and a color index of 1 or slightly lower. Furthermore, he found that 70 per cent of 80 patients with disease of the biliary tract had red blood cell counts below 4,000,000 per cubic millimeter and that in 42 of the patients the level was between 3,000,000 and 4,000,000. In contrast to these data, it was found that in 79 patients with peptic ulcer the red blood cell count was below 4,000,000 per cubic millimeter in only 9 instances. He emphasizes that although a form of hyperchromic anemia is known to occur in major hepatic disease, such as cirrhosis, the comparative frequency of such a blood picture in ordinary biliary dysfunction has received little attention. This type of anemia, according to Colvin, responds to intramuscular injection of liver extract. In addition to the hematologic improvement, it is reported that there is relief from the symptoms classified as those of chronic indigestion. Hence the author suggests that some factor may be present in liver extract which influences the functional disturbances of the biliary system. We agree that every patient with disease of the liver or the gallbladder should have a complete examination of the blood. Certainly if macrocytic anemia exists liver extract should be given intramuscularly. In a certain percentage of cases there will be a response to this form of therapy, because, as the author recognizes, some of these cases will be instances of true pernicious anemia. In the others a trial of therapy is merited, but it has not been our experience that macrocytic anemia

10. Copenhaver, W. M.: Liver Extirpation and Implantation in Amblystoma Embryos with Particular Reference to Blood Formation, Am. J. Anat. **73**:81, 1943.

11. Colvin, M. G.: Hyperchromic Anemia in Chronic Biliary Dysfunction: Response to Liver Therapy, Pennsylvania M. J. **46**:1168, 1943.

associated with disease of the gallbladder and amenable to therapy for pernicious anemia is commonly encountered.

A case is reported by Hill and Hausmann [12] of a 52 year old man in whom anemia developed in association with acute infective hepatitis. This patient was found to have a red blood cell count of 2,300,000 per cubic millimeter and a hemoglobin level of 63 per cent approximately nine weeks after the onset of jaundice.. There were slight anisocytosis, macrocytosis, hyperchromia, polychromasia and a few nucleated red blood cells in the circulating blood. The white blood cell count was 3,200 per cubic millimeter, and the differential count was normal. A sternal puncture showed that erythropoiesis was normoblastic. With injection of liver extract intramuscularly, the red blood cell count slowly returned to normal following a slight rise in the number of reticulocytes (maximum 3.2 per cent). It is concluded by Hill and Hausmann that the response to liver extract suggests that the anemia was due to the lack of liver principle; on the other hand, it is conceded that the improvement might have been associated with a spontaneous recovery. They claim, however, that the reticulocyte response favors their view that there was a deficiency of liver principle, which they attribute to the hepatitis.

Additional studies on the nature of the active principle in liver extract have been completed by West and Moore.[13] In studying a liver extract ("No. 31") prepared by Dakin and West in 1936 and three commercial liver extracts by means of the Tiselius electrophoretic cell, they found that the material could be divided into a slow and therapeutically potent component and a fast one which was practically inert. These studies, when combined with preliminary observations on the nitrogen content and the specific rotation, suggest that there may be some correlation between these characteristics and clinical activity. It is hoped that further work may throw some light on this association.

Treatment and Prognosis.—Proteolyzed liver was prepared for use in treating patients with pernicious anemia because it was thought by Davis, Davidson, Riding and Shaw [14] that whole liver might be superior in the treatment of certain types of macrocytic anemia, such as those which occur in sprue, pregnancy and nutritional deficiency states in the tropics. Furthermore, it was hoped that this form of therapy might be beneficial to patients with some of the refractory anemias which have been shown to be amenable to treatment with whole liver when given orally. "Proteolyzed liver" was prepared by employing the enzyme papain at the natural p_H of minced liver, which is approximately 5.6. In this way it was thought that the danger of destroying the active principle by exposure to acid or alkaline conditions could be avoided. The product obtained was a dry, sterile, granular, light brown powder, which was soluble in hot or cold water. It was estimated that 1 ounce (30 Gm.) of the powder thus obtained was derived from approximately 6 ounces (180 Gm.) of "wet" liver, after allowance for the losses due to the mechanical process. It was administered after being dissolved in warm water and adding salt and pepper to taste, which made a "quite palatable" beverage. From 2 drachms to 1 ounce (4 to 30 Gm.) was given daily in two doses. There was a satisfactory result in all of the 5 treated patients, as measured by the increase in the red blood cell count and the reticulocytes. The average rise in the red blood cell count was 940,000 per cubic millimeter in the first two weeks and 1,740,000 during the first three weeks. The rise in the reticulocyte count in the 4 of the 5 cases in which it was determined was adequate. The authors concluded that the average effective daily dosage was 2 drachms (8 Gm.), which is the amount derived from less than 2 ounces (60 Gm.) of liver. They state that since ½ pound (185 Gm.) of liver is the minimum daily amount considered necessary to produce a satisfactory response in pernicious anemia, it would seem that the proteolyzed liver is relatively much more effective. In discussing the possible advantages of such a product, the authors suggest that it may be useful if it can be marketed at a cost which compares favorably with that of liver extract for parenteral use. Such a preparation could be used for persons situated in circumstances rendering regular injections inconvenient or for persons who object to injections. Also it would be useful for persons who are allergic to injected liver extract. Furthermore, such a method of therapy may be of value for refractory megaloblastic anemia of idiopathic origin, and the active factors present in proteolyzed liver may be effective against anemia with a normoblastic bone marrow.

12. Hill, J. N., and Hausmann, W.: Liver Deficiency Anaemia in a Case of Acute Infective Hepatitis, Brit. M. J. **2**:262, 1943.

13. West, R., and Moore, D. H.: Electrophoretic Pattern of Hematopoietic Liver Extract, Tr. A. Am. Physicians **57**:259, 1942.

14. Davis, L. J.; Davidson, L. S. P.; Riding, D., and Shaw, G. E.: Treatment of Pernicious Anaemia with Experimental Proteolysed Liver Preparation: Preliminary Observation, Brit. M. J. **1**:655, 1943.

Jenks [15] states that a satisfactory explanation of the so-called spontaneous remissions has never been made. He reviews the literature and lists the lengthy remissions which have been reported. Although they are extremely rare, he has collected a number which have had a duration varying from five to seventeen years. He reports an undoubted case of pernicious anemia in which a remission persisted from 1926 to 1941, fifteen years. At the end of this interval there was a relapse, but a therapeutically induced remission has been maintained since then by means of liver therapy.

Allergy Following the Use of Injectable Liver Extract.—Attention is again directed by Delikat [16] to the observation that patients with pernicious anemia who have been treated with liver extract intramuscularly may become intolerant to the preparation. In her experience this has occurred in 14 patients with pernicious anemia out of 200 who have been treated during the past fifteen years at the Royal Hospital, Wolverhampton, England. None of the patients gave a history of previous allergic manifestations. Evidences of hypersensitivity ranged from slight local reactions at the site of the injections to severe constitutional symptoms characterized by general urticaria, vomiting, failure of vision and attacks of typical asthma. The patients with milder symptoms responded to ephedrine given orally, and those of the more severe ones, to injections of epinephrine. It was found that the sensitivity extended to all brands and types of liver extract; hence attempts to carry on treatment with preparations other than those responsible for the sensitization were uniformly unsuccessful. In some cases the allergic manifestations were only transient, while in others they persisted and made it necessary to give the medication by mouth. Three cases were reported in which a sensitivity to parenteral injection of liver extract developed. It was possible to desensitize 2 of the patients by giving small doses over a period of two weeks. For the third patient, this method was not tried but treatment was carried on by injection of small doses every two days. Delikat considers that there is every reason to suppose that the intolerance is due to "allergic" sensitization, the liver acting as an antigen. Of the various methods suggested for the management of such patients, Delikat believes that the parenteral injection of liver extract in divided and increasing doses is the most rational. It is of interest to note that in 1 patient of the 3 studied the cutaneous tests for sensitivity to liver extract gave negative results. It must be concluded, therefore, that such tests cannot be relied on to indicate intolerance.

Morgans,[17a] in commenting on the article by Delikat, gives the details relating to a patient under his observation who died as a result of sensitivity to liver extract. The patient was a man 83 years of age who had been under treatment for pernicious anemia for about five years. He became intolerant to the injections after about four years of treatment and at that time had one severe attack of dyspnea and cyanosis with partial collapse which was relieved by epinephrine. After this liver extract was given orally, rather ineffectively. Again liver extract was given parenterally in a dose of 1 cc. Except for slight cutaneous irritation, this was well tolerated. Four weeks later a dose of 2 cc. was given. This was followed in twenty minutes by death from acute respiratory failure.

A second comment with reference to the article by Delikat appears in the "Letters, Notes and Answers" department of the *British Medical Journal* for July 3, 1943.[17b] The letter pertained to a woman aged 59 with pernicious anemia who had done well when liver extract was given every few months, because she "was too lazy to have it oftener." Three months before inquiry, however, she almost succumbed to an allergic reaction. Desensitization had been begun with small doses, which had almost reached the therapeutic dose of 2 cc. The anonymous writer desired to know the answers to the following questions: 1. Is there danger that the patient may become resensitized when therapeutic doses are given again at intervals of a month or so? 2. If she gets careless and omits treatment for two or three months should she give herself 2 or 3 minims (0.12 or 0.18 cc.) at, say, 10:00 a. m., repeat at 10:15 a. m., repeat at 10:30 a. m. and, if there is no trouble, have the rest of her dose at 11:30 a. m.? The unsigned answer to these questions states that the complete disappearance of allergy is rarely if ever accomplished by any type of therapy and that the term hyposensitization is therefore preferable to desensitization. It is stressed that the continued injection of the specific allergen binds or exhausts the humoral, cellular and skin-sensitizing antibodies, so that the allergic reaction cannot occur. If treatment is interrupted, the react-

15. Jenks, A. L., Jr.: Pernicious Anemia: Report of Case with Fifteen Year Remission, J. Iowa M. Soc. **33**:112, 1943.

16. Delikat, E.: Intolerance to Liver Extract in Pernicious Anaemia, Brit. M. J. **1**:539, 1943.

17. (*a*) Morgans, C. C.: Intolerance to Liver Extract in Pernicious Anaemia, Brit. M. J. **1**:613, 1943. (*b*) Sensitivity to Liver, letter and answer, ibid. **2**:29, 1943.

ing antibodies may form again within a few weeks. For this reason it is preferable that the inoculation should be given once every two weeks. It is considered that when one is treating a patient with pernicious anemia who has become sensitive to liver it is hazardous to extend the interval beyond three weeks. Furthermore, the author wisely counsels that if the patient should go more than a month without treatment it would be inadvisable to allow her to inject the medicament herself. It is stated that in cases of this kind the full technic of desensitization by the "rush" method should be performed again. They urge that the patient be under constant supervision and that solution of epinephrine hydrochloride in a syringe and a tourniquet be at hand when the injections are given. Finally, it is advised that patients who have become sensitive should be told to take whole liver by mouth as frequently as possible, since this may produce a mild desensitization.

In a communication to the *British Medical Journal*[18] Merriman emphasizes the following points relative to sensitivity to liver extract: 1. Sensitivity toward liver extract is rare when the large amount which is used in practice is considered. 2. Sensitivity is usually acquired during treatment or maintenance. 3. Primary idiosyncrasy is rare, and there is usually either history of allergy or one of previous reaction to injections of a similar nature. 4. Once a patient is sensitive to liver protein, changing the brand of extract has little effect. 5. Desensitization can usually be accomplished simply. He recommends the following dosage: administration of 0.2 cc. intradermally, followed by 0.5 cc. intramuscularly twenty minutes later and the remainder of the dose intramuscularly after a further twenty minutes. 6. Preliminary cutaneous tests should be made in patients with an allergic history. Those showing a strong cutaneous reaction should have the simultaneous administration of epinephrine with the liver principle. Corner,[18] in commenting on these statements, recommends injection of 0.5 cc. of 1 : 1,000 solution of epinephrine hydrochloride five or ten minutes before the injection of liver extract in order to prevent reactions. According to him, this should eliminate the development of allergy and may be continued for about six times which in the ordinary case of pernicious anemia would be in a period of five or six months. Thereafter he suggests that ephedrine, in doses of ¼ to ½ grain (0.015 to 0.03 Gm.), be given an hour before the injections for another six months. He believes that after this interval the use of ephedrine can probably be discontinued, as there seems to be a natural tendency for the sensitivity to disappear..

The case of a 48 year old man with lymphosarcoma of the stomach and macrocytic anemia in whom an allergic reaction developed after injection of liver extract is reported by Warburton.[19] The patient was given liver extract parenterally every three or four days for four injections. After an interval of three weeks, when liver extract was again given a typical anaphylactic reaction developed. The symptoms persisted for about one hour. The patient was found to be sensitive, as determined by the cutaneous tests, to various brands of liver extract, regardless of whether they were made from pork or from beef liver. There was no sensitivity to thiamine hydrochloride, which had been present in the liver extract responsible for the reaction. There were no evidences of sensitivity to pork and beef muscle extract when cutaneous tests were done with these substances. The cutaneous tests continued to elicit positive reactions to both pork and beef liver at the end of three months and again in twelve months. An unsuccessful attempt was made to sensitize a person to liver extract who was already sensitive to spring grasses. The patient was given 1 cc. of liver extract (Lederle's) every five days for five doses. After an interval of four weeks injection of liver extract was not productive of anaphylactic manifestations.

Feinberg, Alt and Young[20] give a review of their experience with allergy following the use of injectable liver extracts. According to them, it would seem that sensitivity to these preparations is fairly common. They found that it existed in 6, or 12.5 per cent, of 48 patients. In approximate order of increasing severity the allergic manifestations consisted of itching of the skin, particularly of the palms, flushing of the face, nausea and slight faintness, generalized urticaria and angioneurotic edema, asthma and systemic reactions. Their patients did not experience anaphylactic shock, as has been described by others. Three of their patients had had long established chronic atopic manifestations, and another had had some recurring urticaria. It is their opinion that a long period between injections (three weeks) favors the establishment of sensitization. All of the patients gave the immediate whealing type of cutaneous

18. Merriman, B. M., and Corner, W.: Allergy to Liver Extract, Brit. M. J. **1**:528, 1943.

19. Warburton, R. T.: Acquired Sensitivity to Injectable Liver Extracts, Ohio State M. J. **39**:905, 1943.

20. Feinberg, S. M.; Alt, H. L., and Young, R. H.: Allergy to Injectable Liver Extracts: Clinical and Immunological Observations, Ann. Int. Med. **18**:311, 1943.

(scratch) and intracutaneous reactions with the commercially prepared injectable liver extracts. Both beef and pork liver extracts elicited positive reactions, as did the horse liver extract, although the reaction to the latter was negative in 1 case and in all instances the reactions to it were weaker. Observations were made which led the authors to believe that the antigen responsible for the reaction was not the liver protein nor was it closely bound to it. A fraction of liver extract which was free from protein elicited a positive reaction when used in a cutaneous test in a dilution of 1 : 1,000,000. The antigen seems to be intimately associated with the antianemic fraction. The authors state that several solutions to the problem are open to the patient who shows a distinct allergic systemic reaction. For some of the patients with mild reactions injections may be continued with no ill effects. In some instances the difficulty may be solved by a temporary discontinuance of the injections. In 1 case the problem was met by changing to a liver extract which had been prepared from beef. It is possible that in the cases of more severe reactions a course of desensitizing injections may produce a high level of tolerance. It may be, however, that in some patients it will not be possible to inject therapeutic doses of liver extract at any time. In such cases the treatment must be with liver extract given orally, which fortunately is well tolerated at all times.

Achlorhydria and the Efficacy of Dilute Hydrochloric Acid.—It has long been known that patients with true addisonian pernicious anemia do not have free hydrochloric acid in the gastric secretions. This condition, it is commonly believed, exists from birth, and despite effective antianemia treatment and a disappearance of all gastric complaints, the free acid never returns in the stomach contents. With regard to achlorhydria in patients with pernicious anemia there are at least two practical questions. One is concerned with the relation of the achlorhydria to symptoms and the other with the degree of effectiveness of replacement therapy with the official dilute hydrochloric acid of the United States Pharmacopeia. In answer to the first question, we consider that the presence of achlorhydria alone does not necessarily mean that the patients will have any symptoms which can be attributed to it. This is thought to be true because patients with pernicious anemia are known to have such a condition for many years before the onset of the symptoms of the disease, and yet they have no gastric complaints. Furthermore, the gastrointestinal manifestations disappear with effective anti-pernicious-anemia therapy and a return of the red blood cell count to normal, but the achlorhydria persists. Reliable studies are available which indicate that achlorhydria is not uncommon in otherwise normal persons. Koehler and Windsor [21] cite figures from Bennett and Ryle [22] and Vanzant and his associates,[23] who observed that 4 per cent of normal healthy male medical students had achlorhydria and that 25 to 35 per cent of patients between the ages of 60 and 70 years without gastric disease had a similar condition. A more recent study, in 1939, by Ruffin and Dick,[24] showed that achlorhydria was present in 10 per cent of 2,877 patients after stimulation with histamine and in 25 to 30 per cent of patients more than 45 years of age.

The studies of Koehler and Windsor [21] have an important bearing on the therapeutic value of dilute hydrochloric acid. They found that the addition of the usual amount of acid employed in replacement therapy to a representative ground meal in vitro had little relative effect on the p_H of the meal, owing to the buffer action of the food. They conclude that the amount of acid necessary to bring the p_H of the meal to a normal post-meal range (p_H 1.6 to 1.8) or for peptic activation (below p_H 2.0) is of such magnitude that practical aspects preclude its administration. The dose of U. S. P. hydrochloric acid would be 35 cc. They also estimate that even twenty 420 mg. capsules of glutamic acid hydrochloride given with a meal would fail to produce normal acidity or activate pepsin. It is estimated that the amount of hydrochloric acid secreted by the stomach for an average meal must be in excess of 104 cc. of the normal acid or 35 cc. of U. S. P. dilute or 3.8 Gm. of hydrogen chloride, as calculated from their data. We are in accord with the generally accepted view that dilute hydrochloric acid therapy is of no value as now given and that the theoretic amounts which should be administered in order to approximate the amounts secreted by the stomach normally cannot be employed for practical rea-

21. Koehler, A. E., and Windsor, E.: The Effectiveness of Replacement Therapy in Achlorhydria, Ann. Int. Med. **18**:182, 1943.

22. Bennett, T. I., and Ryle, J. A.: Studies in Gastric Secretion: Study of Normal Gastric Function Based on Investigation of One Hundred Healthy Men by Means of Fractional Method of Gastric Analysis, Guy's Hosp. Rep. **71**:286, 1921.

23. Vanzant, F. R., and others: Normal Range of Gastric Acidity from Youth to Old Age: Analysis of 3,746 Records, Arch. Int. Med. **49**:345 (March) 1932.

24. Ruffin, J. M., and Dick, M.: Significance of Gastric Acidity After Histamine Stimulation: Statistical Study of 2,877 Gastric Analyses, Ann. Int. Med. **12**: 1940, 1939.

sons. We have never been able to convince ourselves that 4 cc. of dilute hydrochloric acid U. S. P. when given three times daily has any effect on the patient's gastric complaints, unless occasionally slight improvement may follow, apparently on a psychic basis. It is no longer our custom to administer this type of medication routinely. For occasional patients in whom the gastrointestinal symptoms do not subside with liver therapy, it is worthy of a trial.

Changes in the Nervous System in Pernicious Anemia.—Dynes and Norcross [25] emphasize that in recent years, neuropathologic investigations have confirmed the presence of involvement of peripheral nerves in many patients with pernicious anemia who have neurologic complications. Generally the clinical diagnosis of peripheral neuritis is made on the basis of pain referable to peripheral nerves, dysesthesia or paresthesia, tenderness on pressure over the nerve trunks or muscles, usually with evidence of muscular weakness as the disorder progresses, and a loss or diminution of tendon reflexes, starting distally. There is also a tendency to loss of superficial hyperesthesia to pain and touch. When the condition is mild, one has fewer diagnostic criteria on which to base an opinion. In a study of 92 patients with pernicious anemia, these observers found that approximately 23 per cent had unmistakable peripheral neuritis in combination with combined system disease. An additional 24 per cent had the clinical signs of combined system disease without peripheral neuritis, while the remaining 53 per cent showed evidence of pernicious anemia without clearcut neurologic signs. In the attempt to discover a cause for the peripheral neuritis, it may have been important that 50 per cent of the neuritic group had definite gastrointestinal symptoms on entry to the hospital, as compared with 21 per cent of those not showing neuritic manifestations. The treatment recommended for patients demonstrating severe neurologic complaints is 20 U. S. P. units (3.3 U. S. P. units per cubic centimeter) of liver extract given intramuscularly daily for several weeks, with a continuation of this dose every second day for several months. Thereafter 20 U. S. P. units should be administered at least twice a week until the neurologic manifestations have improved definitely or cleared entirely. Large doses of a potent vitamin B complex preparation are always given as supplementary therapy. The authors found no evidence to indicate that crude liver extracts are more effective in the treatment of the neurologic complications than concentrated preparations. Less concentrated brands have been used by the authors, however, because they are cheaper. The results attained were better in patients in whom there was evidence of peripheral neuritis as well as combined system disease. Of 21 patients with both complications, 16 responded well, with pronounced regression of symptoms and unmistakable reversion of signs toward normal.

Relationship of Pellagra and Sprue to Pernicious Anemia.—After a careful consideration of the relationship between pellagra, sprue and pernicious anemia, Harris and Harris [26] conclude that they are separate and distinct disease entities but that there are a number of reasons for regarding them as allied nutritional disorders. There are many symptoms which may be common to the three conditions. The oral and gastrointestinal symptoms in pellagra (without cutaneous lesions), pernicious anemia and sprue may be indistinguishable in cases in which there is a macrocytic anemia. In the opinion of the authors, hepatic insufficiency, perhaps associated with fatty degeneration of the liver, appears to be a factor in the genesis of pellagra, pernicious anemia and sprue. They report cases in which it is claimed that pellagra and pernicious anemia, and pellagra, sprue and pernicious anemia existed in the same patient. According to them, this suggests a common cause. The close relationship between the three diseases is emphasized by the following statement of the authors:

> . . . given an adult patient with achlorhydria, stomatitis, diarrhea, mental depression, and the motor manifestations resulting from the involvement of the lateral and posterior columns of the spinal cord and severe anemia, it may be impossible to make a positive diagnosis of pellagra, pernicious anemia or sprue. The addition of a symmetrical, bilateral, pigmented, exfoliative, erythrematous dermatitis on the dorsal surfaces of the hands and feet to symptoms which may be common to sprue and pernicious anemia enables the clinican to make a diagnosis of pellagra; while the large, fat, fermenting, pasty, clay-colored stools in a patient with stomatitis, diarrhea, and severe anemia, may be the only pathognomonic difference between sprue and pernicious anemia. The patient with stomatitis, diarrhea, mental, sensory and motor symptoms, and anemia, without skin lesions, who resides in a community in which pellagra exists would be regarded as a probable pellagrin. Likewise, the patient with the same symptoms, who resides for instance in Porto Rico in which sprue is endemic, with only an occasional case of pellagra, would be diagnosed as having sprue.

25. Dynes, J. B., and Norcross, J. W.: Peripheral Neuritis as a Complication of Pernicious Anemia and Combined System Disease, J. A. M. A. **122**:586 (June 26) 1943.

26. Harris, S., and Harris, S., Jr.: Pellagra, Pernicious Anemia and Sprue: Allied Nutritional Diseases, South. M. J. **36**:739, 1943.

Hanes [27] considers that celiac disease bears the same relationship to sprue that cretinism does to myxedema. In adult sprue, of either the "tropical" or the "nontropical" type, which he regards as identical, the response to parenterally administered liver extract, with a diet low in fats and rich in proteins and vitamins, is prompt and dramatic in a great majority of patients. Likewise celiac disease has been shown to respond satisfactorily to parenterally given liver extract when the vitamin B complex is added. The diagnostic requirements of the syndrome to which Hanes adheres rigidly are as follows: (1) steatorrhea, (2) loss of weight, (3) low dextrose tolerance curve, (4) anemia and (5) hypochlorhydria or achlorhydria. He considers it impossible in some cases to establish the diagnosis of sprue without a quantitative estimation of fat in the stools. For his series of patients with sprue, the average amount of fat in the dried stools was 48.5 per cent, whereas for normal persons it does not exceed 15 per cent. He states that the following differential possibilities must be considered in the diagnosis of the sprue syndrome: (1) pernicious anemia, (2) multiple avitaminoses, (3) pancreatic disease, (4) tabes mesenterica, (5) gastrocolic fistula, (6) anorexia nervosa and (7) Simmonds' disease (hypopituitary cachexia). The blood in sprue practically always exhibits a macrocytic, hyperchromic anemia which cannot be distinguished by studies either of the peripheral blood or of the bone marrow from the hematologic picture of pernicious anemia. The bone marrow of children, however, seldom reacts in a macrocytic, hyperchromic manner to any injury, and according to the author it is not surprising that a blood picture of this type is rare in celiac disease. An important point made by Hanes in the differential diagnosis of sprue from pernicious anemia is that histamine-refractory achlorhydria does not occur in patients with sprue more often than in normal persons. In his 56 cases, normal values were found in 22 per cent, hypochlorhydria in 57 per cent and achlorhydria in 21 per cent. He emphasizes, therefore, that in 79 per cent of the cases of sprue syndrome the differential diagnosis could be made by the results of the gastric analysis alone. Although the treatment of sprue as just outlined is usually satisfactory, Hanes reports 4 patients who were refractory to it.

27. Hanes, F. M.: Diagnostic Criteria and Resistance to Therapy in the Sprue Syndrome, Am. J. M. Sc. **204**: 436, 1942.

It is emphasized by Hansen-Pruss [28] that the clinical picture of the sprue syndrome is remarkably pure despite the fact that chemical studies may reveal multiple vitamin deficiencies. In a study of 66 cases of sprue by this observer, no instance of pellagra, beriberi or scurvy has been found accompanying the sprue state. One patient, however, who is the subject of the report, a man aged 39, had sprue and later reappeared at the hospital, after the evidences of sprue had subsided, with the typical clinical findings of pellagra. There seems to be no doubt that this patient had sprue when first admitted to the hospital in January 1941, and it is likely that the symptoms which he had experienced in the previous five years were due to this condition. The diagnosis of sprue was established on the basis of the history, the striking loss of weight, the steatorrhea, the flat dextrose tolerance curve and the macrocytic anemia (red blood cells 2,600,000 per cubic millimeter, hemoglobin 10.1 Gm. per hundred cubic centimeters [65 per cent], mean corpuscular volume 108 cubic microns) and the megaloblastic bone marrow. The patient responded satisfactorily to parenteral administration of liver extract, as shown by the gain in weight and the cessation of the steatorrhea. In the interim between the first and the second admission to the hospital, the latter in July 1942, the patient had gastric complaints and was found to have a pyloric obstruction, thought to be due to a stenosing duodenal ulcer, which caused a 65 per cent obstruction. With this the classic signs of pellagra appeared, but the blood remained normal. It is of interest to note that the pellagra developed while the patient was receiving large doses of liver extract parenterally over a period of months. The author concludes that the sequence of events suggests that refined liver extract does not contain the pellagra-preventive factor. When the patient was treated with nicotinic acid, the clinical evidences of pellagra subsided.

In an article by Barker [29] the clinical features, the differential diagnosis and the treatment of sprue are discussed. Reference here, however, will be made only to the changes in the blood. He points out that anemia is a common finding in sprue, although it is by no means essential for making the diagnosis. It may be present in only about one third of the patients when they first come under observation. In general,

28. Hansen-Pruss, O. C.: Pellagra Developing in a Patient Receiving Liver Extract Parenterally for Sprue, South. M. J. **36**:440, 1943.

29. Barker, W. H.: Sprue, M. Clin. North America **27**:451, 1943.

it may be said that the longer the duration of the disease and the more severe the diarrhea, the more likely is anemia to be present. When present in uncomplicated sprue, it is almost invariably macrocytic and hyperchromic. Only occasionally is a normocytic or hypochromic variety present. The blood picture may simulate closely that of pernicious anemia. Erythrocyte counts below 1,000,000 per cubic millimeter have been reported, and the mean corpuscular volume may be as high as 150 cubic microns and the color index above 1.5. If a hypochromic, microcytic anemia is encountered in sprue, one should be suspicious of chronic loss of blood through the action of such a parasite as Endamoeba histolytica or the hookworm. According to Barker, in nontropical sprue the anemia may be macrocytic and hyperchromic but more frequently it is normocytic or hypochromic, microcytic. It is his belief that such anemia must result from inadequate intake or defective absorption of iron, for there is usually no evidence of chronic loss of blood. In the majority of cases, in his opinion, there is probably a deficiency of both iron and the "liver principle," with the features of one or the other type of deficiency predominating. The leukocyte count is usually normal or reduced, and even pronounced leukopenia is not uncommon. There is nothing characteristic about the differential formula, although relative lymphocytosis is frequently observed.

In a general article on the physiologic interpretation of the clinical changes in sprue, Rice [30] discusses fully the hematologic aspects of the disease. He found that the blood picture in sprue, as shown in 365 cases reported in the literature, was as follows: The red blood cell count was below 4,000,000 per cubic millimeter in over 95 per cent of the cases, with a count as low as 600,000 having been reported. The hemoglobin content was below 10.2 Gm. per hundred cubic centimeters of blood in 51 per cent of the cases. In over 90 per cent macrocytic anemia was present; the anemia was occasionally normocytic but almost never microcytic. Usually the hyperchromic form was reported, but occasionally the normochromic or hypochromic variety was observed. Pronounced variation in the size and shape of the erythrocytes was almost universally noted, with many oval cells and occasionally primitive nucleated red blood cells. Leukopenia, often with relative lymphocytosis, was common. The mean reticulocyte count in 100 cases was 1.8 per cent, and the mean platelet count was 142,000 per cubic millimeter. The blood picture often resembles that of addisonian pernicious anemia, with a few variations from the typical picture. After discussing the literature dealing with the cause of the anemia in sprue, the author concludes that the studies of Castle and his associates merit the conclusion that the anemia of sprue is due to the variable participation of three causes: (1) the lack of a factor (extrinsic) in the diet, contained in meat, eggs and whole cereal, but not as yet identified; (2) the failure of the secretion of a factor (intrinsic) in the normal gastric juice, presumably identical with the substance usually lacking in addisonian pernicious anemia in relapse, and (3) difficulty with the absorption of the products of this reaction from the intestinal tract.

It is suggested on the basis of the work of Miller and Rhoads in 1935 that in some cases of sprue diets deficient in the extrinsic factor may explain the origin of the deficiency of the intrinsic factor which has been observed. The literature is cited in support of the belief that the ability to elaborate the intrinsic factor in sprue is a functional one alone, as distinguished from the functional and anatomic changes of the gastric mucosa which are seen in pernicious anemia. According to Rice, studies of the bone marrow have revealed that in pernicious anemia and sprue there is an identical picture of failure of erythropoiesis. It is to be concluded, therefore, that in both conditions the immediate cause of the anemia is a deficiency of the "erythrocyte-maturing factor" contained in liver extract, which is necessary for the normal formation of erythrocytes from the primitive bone marrow cells. Reference is made to the observation by Castle and Rhoads and their associates in 1935 that, as in certain patients with pernicious anemia, after the administration of iron to some patients with sprue, liver therapy may be followed by an additional hemopoietic response. These authors surmised from this that there may be a deficiency of iron in some patients with sprue due to a decreased dietary intake, decreased gastric acidity or intestinal impermeability, and suggested that this would explain the hypochromic anemia which is seen in a small percentage of patients with sprue.

Miscellaneous Observations Concerning Pernicious Anemia.—A group of young adults with atypical pernicious anemia is reported on by Schwartz and Legere,[31] and the similarities and dissimilarities between the usual case of the dis-

30. Rice, M. E.: A Physiological Interpretation of the Clinical Changes in Sprue, J. Bowman Gray School Med. **1**:144, 1943.

31. Schwartz, S. O., and Legere, H.: Atypical Pernicious Anemia of Young Adults, Am. J. M. Sc. **206**:1, 1943.

ease and those presented are discussed. Their series consisted of 9 women, 5 of whom were Negroes, all under 35 years of age, who had illnesses characterized by a variable duration, loss of weight, fever, jaundice, anemia, cardiac murmurs and hepatomegaly or splenomegaly or both. Macrocytic anemia, achlorhydria and a specific favorable response to liver therapy were demonstrated at some time in all patients. Typical relapses occurred in 6 of the patients when liver therapy was withheld. The shortest time between relapses was two and a half months and the longest fifteen months. The authors state that the manifestations of the condition in the 9 patients differed sufficiently from those of typical pernicious anemia to cause diagnostic difficulties. The most significant variations were the occurrence in a younger age group (7 of the 9 being between 25 and 31 years of age), the frequency in Negroes (5 of the 9 patients), the apparent acuteness of the onset, the misleading prominence of cardiac symptoms, the febrile course so strongly suggestive of infection and the conspicuous paucity of neurologic complaints. To the reviewers, the most helpful clinical manifestations which would cast some doubt on the diagnosis of true addisonian pernicious anemia in such patients would be the high incidence in Negroes, the presence of a palpable spleen in 7 of the 9 patients and the apparent absence of the symptoms of glossitis and paresthesia. The presence or absence of these highly significant symptoms is not emphasized by the authors. They stress, properly, the necessity of including pernicious anemia in the differential diagnosis of a severe anemia, regardless of the age of the patient.

An interesting case of macrocytic anemia in a patient who succumbed to acute pulmonary tuberculosis is reported by Apfelbach.[32] The macrocytic anemia, leukopenia, achylia and paresthesia, the megaloblastic bone marrow seen on sternal puncture and the striking response to liver extract all suggested strongly the diagnosis of pernicious anemia. There were two points of special interest in the case history. First, the spleen was palpable, which is not common in patients with pernicious anemia. It could be felt, however, not because it was actually enlarged but because it was displaced by a cyst of the kidney which had nothing to do with the essential disease. Second, it is rare to have widely disseminated tuberculosis in a patient with pernicious anemia. This was the cause of death of this patient.

32. Apfelbach, C. W.: Macrocytic Anemia and Acute Pulmonary Tuberculosis, Illinois M. J. **83**:137, 1943.

Procopie and Armington[33] observed a pregnant woman in whom preeclamptic toxemia and pernicious anemia developed. The patient, an American housewife aged 21, had a red blood count of 2,100,000 per cubic millimeter, with a hemoglobin content of 52 per cent and macrocytosis. There was a strikingly favorable response of the blood to liver extract given intramuscularly. As the patient had an obviously deficient food intake, it seems to us likely that the macrocytic anemia which responded so remarkably to liver extract was due to an inadequate protein intake, as emphasized by Bethell in recent years.

Two separate studies on patients with pernicious anemia have been reported by Stasney and Pizzolato and one by Stasney and McCord. These appeared in the December 1942 number of the *Proceedings of the Society for Experimental Biology and Medicine* and unfortunately were overlooked in the 1943 review of diseases of the blood. The first studies[34] had to do with the fluctuation in the number and volume of nucleated red blood cells in the sternal marrow of patients with pernicious anemia, as determined by repeated aspirations of the bone marrow following treatment. Observations made at twenty-four hour intervals before and after liver-induced remissions in 16 patients with addisonian pernicious anemia revealed that there was a pronounced fluctuation of the total number and volume of the nucleated elements. Six to twenty-four hours after the first injection of liver extract the majority of the patients showed a striking decrease in the number of nucleated cells. There was a rapid disappearance of the megaloblasts within twenty-four to forty-eight hours, which was associated with the presence of an increased number of early normoblasts. Further analysis showed that the fluctuations of the nuclear elements were almost entirely due to the periodic increase and decrease of cells of the normoblastic series. The increase in the reticulocytes in the marrow preceded, or was simultaneous with, the increase in these same cells in the peripheral blood. During the period from ninety-six to one hundred and sixty-eight hours after the institution of liver therapy, there was at times almost a complete depletion of normoblasts in the marrow. The extent of the fluctuations in the number of nucleated red blood cells appeared to be independent of the amount of liver which was administered.

33. Procopie, G., and Armington, C. L.: Pregnancy Complicated by Preeclamptic Toxemia and Pernicious Anemia, J. Indiana M. A. **35**:466, 1942.

34. Stasney, J., and Pizzolato, P.: Serial Bone Marrow Studies in Pernicious Anemia: I. Fluctuation in Number and Volume of Nucleated Cells, Proc. Soc. Exper. Biol. & Med. **51**:335, 1942.

In a later communication [35] Stasney and Pizzolato report studies on the correlation between the number of nucleated red blood cells in the bone marrow, as determined by sternal puncture, and the level of the uric acid in the urine and in the blood. The blood uric acid was determined daily for 15 patients with addisonian pernicious anemia after the administration of liver extract, according to the method of Folin. In 3 cases the amount of uric acid in the urine was also determined. It was found that there was a definite increase in the uric acid level in the blood and in the urine simultaneous with the diminution of the normoblasts in the bone marrow and with the increase of reticulocytes in the peripheral blood. With the technic used, it was considered that 2 to 4 mg. of uric acid per hundred cubic centimeters of blood was the normal range. In the 24 observations on patients with pernicious anemia in relapse, it was found that the blood uric acid was between 4.2 and 8.9 mg. per hundred cubic centimeters. The patients with an average of blood uric acid which was already above normal had elevations in the level varying from 5.3 to 10 mg. per hundred cubic centimeters seventy-two to one hundred and twenty hours after the first injection of liver extract.

In a third paper dealing with pernicious anemia, Stasney and McCord [36] observed that protoporphyrin was most regularly present in 133 specimens of sternal bone marrow which contained predominantly normoblastic young red blood cells. A study of material obtained at serial sternal punctures in patients with pernicious anemia who had been given liver extract intramuscularly showed that the appearance of protoporphyrin was coincidental with the increase in the immature red blood cells of normoblastic type in the marrow.

A study of the excretion of the keto acids and the hydroxyphenyl compounds in pernicious anemia is reported by Swendseid, Burton and Bethell.[37] These observers found that patients with untreated pernicious anemia have an increased excretion of keto acids and hydroxyphenol compounds but that after therapy the excretion levels are similar to those of healthy persons. The evidence suggests that the keto acid which is excreted in increased amounts is a hydroxyphenyl compound but that other keto groups or hydroxyphenol groups may be involved. The fall in excretion levels of both the keto and the hydroxyphenyl compounds in patients with pernicious anemia after the institution of liver therapy is simultaneous with the beginning of the reticulocyte response and precedes other changes in the cellular components of the blood.

Hemmeler [38] observed that the iron content of the serum of patients with pernicious anemia was elevated above normal but that with the onset of liver therapy a prompt fall in the serum iron occurred. In the persons in whom an iron deficiency developed after therapy with liver, absorption of iron from the gastrointestinal tract was similar to that in normal persons and in persons suffering from a hypochromic anemia.

General Reviews Dealing with Pernicious Anemia.—The histories of 300 authenticated cases of pernicious anemia were reviewed by Carter and Traut [39] from the standpoint of cardiovascular symptoms and signs. They found that 257 patients had cardiovascular manifestations and 43 did not. The more important findings and their incidence were as follows: angina pectoris, 1 per cent; precordial pain (nonanginal), 12 per cent; dyspnea, 51 per cent; palpitation and tachycardia, 22 per cent; displacement of the left cardiac border, 29 per cent; basal rales, 7 per cent; palpability of the edge of the liver, 26 per cent; tenderness over the liver, 3 per cent; edema of the ankles, 34 per cent; apical systolic murmur, 48 per cent; apical presystolic murmur, 1 per cent; apical diastolic murmur, 2 per cent; basal systolic murmur, 17 per cent; basal diastolic murmur, 2 per cent; aortic systolic murmur, 10 per cent; transmitted murmur, 3 per cent. The authors conclude that in the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. It is their opinion that all of the usual criteria of cardiovascular disease may occur solely as a result of anemia. They also state that the cardiovascular manifestations which are so often present with hematologic decompensation disappear after treatment or during a remission.

Katz [40] presents clinical studies made on 42

35. Stasney, J., and Pizzolato, P.: Serial Bone Marrow Studies in Pernicious Anemia: II. Nucleated Cells and Blood and Urine Uric Acid, Proc. Soc. Exper. Biol. & Med. **51**:338, 1942.

36. Stasney, J., and McCord, W. M.: Serial Bone Marrow Studies in Pernicious Anemia: III. Occurrence of Protoporphyrin in Human Bone Marrow, Proc. Soc. Exper. Biol. & Med. **51**:340, 1942.

37. Swendseid, M. E.; Burton, I. F., and Bethell, F. H.: Excretion of Keto Acids and Hydroxyphenyl Compounds in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **52**:202, 1943.

38. Hemmeler, G.: Reabsorption of Iron in Pernicious Anemia, Helvet. med. acta **10**:23, 1943.

39. Carter, J. B., and Traut, E. F.: Cardiovascular Manifestations in Pernicious Anemia, Arch. Int. Med. **72**:757 (Dec.) 1943.

40. Katz, H. W.: A Study of Pernicious Anemia, Bull. New England M. Center **5**:268, 1943.

cases of pernicious anemia which were selected from the records of routine admissions to the diagnostic ward of the Boston Dispensary and the Joseph H. Pratt Diagnostic Hospital. Of the 9,241 patients, with all types of conditions, admitted to these two institutions from Jan. 11, 1932 to July 7, 1942, 86 had pernicious anemia. This is 0.93 per cent of the total number admitted, or approximately 1 in every 100. About 75 per cent of the patients entered the hospital without the proper diagnosis, the admission diagnosis ranging from psychoneurosis to concussion of the skull. A general review is given of the symptoms, complications and diagnostic features of the disease. It is of interest that gastric analysis was done for 34 of the 42 patients and that free hydrochloric acid was found in the gastric secretions of 1 patient. This patient had all of the essential diagnostic features of pernicious anemia, including a megaloblastic bone marrow. Possibly in exceedingly rare instances free hydrochloric acid may appear in the gastric secretions of a patient with pernicious anemia, but in the thirty years' experience of one of us this has never occurred in any of the large number of patients with pernicious anemia whom he has seen.

Brief reviews of the history, pathology, symptoms, changes in the blood and treatment of pernicious anemia are given by Schwartz [41] and Younge.[42]

HYPOCHROMIC ANEMIA

Incidence in Adults and in Children.—Continued interest in the possible relation of wartime dietary restrictions in Great Britain to the incidence of hypochromic anemia has been shown during the past year. The hemoglobin values of 3,338 persons ranging in age from birth to 55 years were determined and analyzed by Davidson and his associates.[43] The group included 563 infants and preschool children up to 4 years of age, 917 municipal primary school children and 105 private school children of 5 to 12 years, 518 adolescent boys and girls of 13 to 19 years, 620 men and women of 20 to 54 years, 45 multiparous women and 570 pregnant women. The Haldane method of estimation of hemoglobin was employed, according to which 100 per cent is equivalent to 13.8 Gm. per hundred cubic centimeters. By the authors' standards the upper limit of normal for school children and nonpregnant women is 80 per cent, for pregnant women 70 per cent and for men 85 per cent. According to these criteria anemia was found in 39 per cent of municipal primary school children, 5 per cent of private school children, 12 per cent of adolescent girls, 7 per cent of the general group of women, 24 per cent of pregnant women and less than 1 per cent of adolescent and adult males. Except among the municipal primary school children the incidence of anemia does not appear to be higher in the present group, who were studied in Edinburgh in 1942-1943, than in a previously reported group, examined in Aberdeen in 1935.

The possible effect of donation of blood on the hemoglobin level was studied by Bryce and Jakobowicz,[44] who examined 4,110 male and 8,956 female donors between the ages of 18 and 65 years. The average values for the two sexes before withdrawal of blood were, respectively, 15.43 and 13.93 Gm. per hundred cubic centimeters. For a series of 815 males and 2,603 females the average hemoglobin at different ages was determined. The lowest value was obtained for the youngest age group, from 18 to 30 years, whereas the highest average was that of the oldest group, from 50 to 65 years. The same age differences were found for both men and women. There were no significant seasonal variations in the hemoglobin values. For a series of 1,577 men who had given blood on two or more occasions at intervals of not less than three months, no significant differences with respect to the predonation hemoglobin levels were found; but of a group of 3,957 women who had had similar withdrawals of blood, 4.14 per cent had hemoglobin values of less than 11.9 Gm. per hundred cubic centimeters before donation, and this figure increased progressively after three or more withdrawals of blood until it reached 9.75 per cent of those who had made five or more donations.

Barer and Fowler [45] observed a gradually decreasing effect of iron therapy in hastening recovery after repeated donations of blood. They concluded that iron appears to have a stimulating effect on synthesis of hemoglobin as well as acting as replacement therapy.

41. Schwartz, S. O.: Pernicious Anemia, Am. J. M. Technol. **9**:192, 1943.

42. Younge, W. A.: Pernicious Anemia, J. Nat. M. A. **35**:30, 1943.

43. Davidson, L. S. P.; Donaldson, G. M. M.; Lindsay, S. T., and McSorley, J. G.: Nutritional Iron Deficiency Anaemia in Wartime: Haemoglobin Levels of 3,338 Persons from Birth to 55 Years of Age, Brit. M. J. **2**:95, 1943.

44. Bryce, L. M., and Jakobowicz, R.: The Haemoglobin Level in Blood Donors, M. J. Australia **2**:329, 1943.

45. Barer, A. P., and Fowler, W. M.: Effect of Iron on Hemoglobin Regeneration in Blood Donors, Am. J. M. Sc. **205**:9, 1943.

Venesections were performed by Alstead [46] on 48 nonanemic male patients with an average age of 60.3 years, and the recovery rate as measured by the hemoglobin level was observed. After five weeks one half of the patients were still below normal with respect to hemoglobin, and after fifteen weeks recovery was incomplete in 10 per cent. The volume of blood lost did not appear to determine the percentage incidence of anemia, but there was some evidence that the duration of the anemia was proportional to the initial fall in hemoglobin.

Nine cases of hypochromic anemia in males between the ages of 17 and 19 years are reported by Thomson.[47] None had a history of hemorrhage, jaundice or dietary deficiency. All of the patients had smooth, pale skins, and in 4 the tongue was smooth. The spleen was palpable in 5, and spoon nails were present in 4. Gastric analysis revealed achlorhydria in 5 of the patients and marked hypochlorhydria in the remaining 4. Determinations of serum bilirubin and of urine urobilin, the fragility test and the reticulocyte count gave uniformly normal values. Of the 9 patients who were observed after iron therapy, all had responded satisfactorily. There is also included in this report the case of a 45 year old man with a similar type of anemia. The author states that it is of practical importance to determine whether a maintenance dose of iron is necessary when the anemia has been overcome.

The case of a girl of 8 years with severe hypochromic, microcytic anemia and histamine-refractory achlorhydria is reported by Dacie and Ellman.[48] Steatorrhea was not present, and the spleen was palpable. There was a good therapeutic response to the administration of ferrous sulfate, 0.2 Gm. three times a day, with regression of the enlargement of the spleen but persistence of the achlorhydria.

The important question of the possible relationship of deficiencies of the vitamin B complex to the incidence of hypochromic anemia in human beings was investigated by Moore, Minnich, Vilter and Spies.[49] Clinical studies were carried out on 50 adults with hypochromic, microcytic anemia, of whom 32 had clinical manifestations of a vitamin B deficiency disorder and 15 had evidences of inadequacy of more than one member of the B complex. All of the patients showed a hematologic response to iron therapy employed as the sole form of treatment. The metal was usually given in the form of ferrous sulfate, 0.8 Gm. daily. There was no demonstrable effect of brewers' yeast in enhancing the therapeutic efficacy of iron, nor was there any tendency of hypochromic anemia to occur more frequently with any of the three recognized specific deficiency states, attributable to a lack of nicotinic acid, riboflavin and thiamine respectively. The authors observed no instances of hypochromic anemia associated with high values for serum iron, such as might be explained on the basis of pyridoxine deficiency.

Trowell [50] points out that in the tropics anemia is not commonly thought of as due to nutritional deficiency but is considered as a secondary manifestation of a disease, usually parasitic, which is endemic in the region. However, among the native population of Uganda, East Africa, he found clear evidence in many cases of the presence of a dual deficiency, of iron and of the factor protective against nutritional macrocytic anemia. When both of these substances are lacking the resulting blood picture may exhibit puzzling features. Such anemia is usually macrocytic and hypochromic; occasionally it is normocytic, hypochromic; and very occasionally it is microcytic, hypochromic. The color index is not a reliable guide in the recognition of such anemia, since in cases of macrocytosis it may be elevated even in the presence of hypochromia. Measurements of cell diameter are likewise unreliable, since the erythrocytes on dried films prepared on slides are not distributed evenly, with a tendency for the larger cells to accumulate at the tail and thin portions of the film. In addition to the measurement of cell size and of hemoglobin concentration, examination of the stained film is of great aid in the diagnosis of this type of dual deficiency in dimorphic anemia. In the thicker portions of the film small hypochromic cells predominate, whereas in the thin areas larger orthochromic erythrocytes are most numerous. According to the author, in dimorphic anemia there is a mixture of megaloblastic and normoblastic erythropoiesis. In 100 of 174 cases of anemia studied, the disease appeared to be of this type. In cases of such anemia iron deficiency is attributable most frequently to hookworm infection and to a diet of low iron content, whereas macrocytic anemia appears to be due to dietary

46. Alstead, S.: Rate of Blood-Regeneration After Haemorrhage, Lancet **1**:424, 1943.

47. Thomson, M. L.: Hypochromic Anaemia in Adolescent Males, Brit. M. J. **2**:454, 1943.

48. Dacie, J. V., and Ellman, P.: Case of Achlorhydric Hypochromic Microcytic Anaemia in Child 8 Years Old, Brit. J. Child. Dis. **39**:97, 1942.

49. Moore, C. V.; Minnich, V.; Vilter, R. W., and Spies, T. D.: Hypochromic Anemia in Patients with Deficiency of Vitamin B Complex: Response to Iron Therapy With and Without Yeast, J. A. M. A. **121**: 245 (Jan. 23) 1943.

50. Trowell, H. C.: Morphology of Blood in Dimorphic Anaemia, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:151, 1942.

lack of meat and possibly of vegetables. Trowell [51] also reports 163 cases of anemia in natives of Ugańda, of which 111 were instances of macrocytic anemia, 43 of normocytic and 9 of microcytic. Of the cases of macrocytic anemia 31 were of the orthochromic and 80 of the hypochromic type. Orthochromic, macrocytic anemia is attributable either to a single nutritional deficiency or to true pernicious anemia. Of the patients with hypochromic macrocytic anemia 18 were incurable, owing to the nature of their associated diseases, whereas the remaining 62, with intercurrent disease, were succesfully treated. The conditions most commonly found in this group were malaria, helminthic infection, syphilis and yaws. The therapeutic management of these patients included treatment of the associated disease and administration of whole liver orally or crude liver extract by intramuscular injection and of iron salts by mouth.

Three cases of hypochromic anemia associated with hookworm infection which failed to respond to iron therapy are reported by Heilig and Visweswar.[52] In 1 case malarial infection was held responsible for the absence of therapeutic response, and in the others the patients suffered, respectively, with infection of the middle ear and of the urinary tract. The authors state that other forms of infection, including sinusitis, may account for unsatisfactory results in the treatment of anemia due to hookworm disease. In such cases the infections and the anemia should be treated simultaneously.

The role of ascorbic acid in erythropoiesis continues to be obscure. Investigations reported in previous reviews have demonstrated no relationship between ascorbic acid deficiency and iron metabolism, although failure of patients with pernicious anemia to respond to liver extract therapy in the presence of vitamin C deficiency has been reported. Israels [53] examined the bone marrow in 3 cases of scurvy with anemia and found evidence of diminished erythropoiesis in 23. The marrow revealed a general depression of erythropoiesis rather than a failure of maturation at any particular stage of development. There were hyperplasia of erythrocytic marrow elements and recovery from anemia following ascorbic acid therapy in all of the patients.

Peco [54] discusses hypochromic anemia in connection with multiple deficiency states associated with atrophic gastritis. Lack of hydrochloric acid, pepsin, iron and vitamins and impairment of general nutrition are considered of etiologic importance in such anemia, and the possible role of each in the individual patient should be evaluated. The author considers that liver extract may be of value in the treatment of some patients with multiple deficiencies.

The incidence of hypochromic anemia after gastric resection was studied by Hemmeler.[55] He subdivided his patients into women who were menstruating, women who were not menstruating and men. The important factors in the development of anemia appeared to be the part of the stomach removed with reference to the secretion of hydrochloric acid, and the amount of the menstrual flow. After the menopause women were still slightly more prone than men to have anemia after partial gastric resection, which was perhaps attributable to more efficient absorption of iron or to the presence of larger storage reserves of iron in men. In menstruating women hypochromic anemia almost invariably developed after gastrectomy. The author found determinations of serum iron of more value than the blood picture as an indication of eventual iron deficiency. He advocates the treatment of all patients who have had gastrectomy with stable ionizable ferrous salts. In his series of cases of anemia following gastric resections one patient with macrocytic hyperchromic anemia was encountered.

The case histories of 72 patients with esophageal hiatus hernia are reported by Murphy and Hay.[56] Of this series 11 were males and 61 females. The incidence was greatest in the age range of 50 to 70, and the average age of all the patients was 60. Examination of the blood was performed for 67 patients, and of these 7 were found to be suffering with apparently true pernicious anemia, while 2 others had severe macrocytic anemia "which may best be diagnosed as idiopathic macrocytic anemia." There were 40 other patients with some degree of anemia, of whom 16 had a severe form. Gastric analysis were performed for 34 patients, with the finding of achlorhydria in 12, of whom 7 were suffering with pernicious anemia. The authors emphasize the importance of considering hiatal

51. Trowell, H. C.: Case for Recognition of Dimorphic Anaemia as Common Deficiency Anaemia, East African M. J. **19**:268, 1942; Deficiency Anaemias of Malnutrition, Lancet **1**:43, 1943.

52. Heilig, R., and Visweswar, A.: Iron-Refractory Anaemia in Hookworm Disease, J. Trop. Med. **45**:113, 1942.

53. Israels, M. C. G.: Erythropoiesis in Scurvy, Lancet **1**:170, 1943.

54. Peco, G.: Anemia hipocrómica pluricarencial: gastritis atrófica, Día méd. **15**:97, 1943.

55. Hemmeler, G.: L'anémié hypochrome après résection d'estomac, Schweiz. med. Wchnschr. **72**:1105, 1942.

56. Murphy, W. P., and Hay, W. E.: Symptoms and Incidence of Anemia in Hernia at Esophageal Hiatus, Arch. Int. Med. **72**:58 (July) 1943.

hernia in all cases of hypochromic anemia for which no cause is readily demonstrated. Such anemia is usually produced by hemorrhage occurring from ulceration of the esophageal or gastric mucosa or from congestion of the mucous surfaces, produced in either case by mechanical interference by the esophageal hiatus.

Four cases of hypochromic anemia associated with kyphoscoliosis are reported by Reimann.[57] The symptoms are orthostatic and disappear when the patient is reclining. They are produced by compression of the stomach and duodenum, with delayed emptying time, and by compression of the large abdominal vessels with dilation of the stomach vessels. In 1 patient erosions of the gastric mucosa were demonstrated.

The theory of iron as a neutralizer of toxic substances is discussed by Albers.[58] This view, current in the older literature, is supported, in the author's opinion, by clinical experimental evidence which he presents. In infectious and certain neoplastic conditions, notably uterine myoma, iron is believed to neutralize toxins, and it is therefore not available for formation of hemoglobin. In patients under treatment for carcinoma with irradiation, no evidence was found of hemolysis nor was there any increase in the serum iron. Instead, an actual decrease, usually amounting to 50 per cent of the pretreatment level, was observed. The decline in serum iron was attributed to detoxification by the metal of injurious products of the neoplasm released during therapy, and it could be prevented by preliminary administration of large doses of iron. The author considers that hemorrhage is a cause of real or absolute iron deficiency, whereas the apparent deficiency present in cases of infection, myoma or carcinoma is merely relative, since iron is present in adequate amounts but is functionally bound. In such relative deficiency states the serum iron values are normal, although the hemoglobin levels are low. Larger doses of medicinal iron are required to correct anemia resulting from relative iron deficiency, and treatment must be continued for a long time. Albers [59] reviews the iron deficiency states occurring in pregnancy, prematurity and infancy and discusses the inhibition of therapeutic response to iron medication exerted by fever. He points out that iron acts as a building stone, not as a remedy or a stimulant.

57. Reimann, F.: Anämie bei Kyphoskoliose, Gastroenterologia **66**:197, 1941.

58. Albers, H.: Die Bedeutung des Eisenstoffwechsels für die Therapie, Deutsche med. Wchnschr. **68**:160, 1942.

59. Albers, H.: Die Bedeutung des Eisenstoffwechsels für die Therapie, Deutsche med. Wchnschr. **68**:188, 1942.

The indications for iron therapy are reviewed by Schultz [60] with particular reference to the chronic anemia of middle and old age, achylic chloranemia, essential hypochromic anemia and iron deficiency in pernicious anemia.

A series of 177 infants attending a well baby clinic were studied by Brokaw, Sedam and Cassirer.[61] The object of the investigation was to determine the trend of hemoglobin and erythrocyte values throughout the first year of life and to ascertain what effect, if any, was produced by the early introduction into the diet of cereals, vegetables and eggs. A progressive decline in red blood cell and hemoglobin levels was observed from the second to the eighth week of life, with a subsequent increase to the sixteenth week, when the values remained relatively stable throughout the remainder of the first year. During the latter period the average level of the hemoglobin was 10.6 Gm. per hundred cubic centimeters and that of the erythrocyte count was 4,500,000 per cubic millimeter. The comment should be made that the average hemoglobin value found by these authors is appreciably less than that considered optimum by most observers. The subjects of the study were subdivided into three groups, designated as advanced, average and control. To the members of the first group vegetables were given at 8 weeks of age, cereal and egg yolk at 12 weeks and potatoes, meats and fruits after 5 months. The second group received cereals at 12 weeks, vegetables at 16 weeks and potatoes, meats and fruits after 5 months. The control group were retained on breast milk or a formula diet exclusively for six months, when cereals were introduced, followed by vegetables at 7 months and meat and potatoes at 8 months. The authors concluded that the early introduction of cereals, vegetables and eggs had no marked effect on the hemoglobin level or the erythrocyte count of the infants observed.

Mineral Metabolism and Experimental Anemia.—Studies on absorption and excretion of iron by 46 healthy college women were carried out by Marsh, Leverton, McMillan and Underwood.[62] There were 50 separate investigations in all, 33 of them dealing with the amounts of iron

60. Schultz, W.: Zur Frage des Eisenstoffwechsels und der Eisentherapie vom Standpunkte der Inneren Medizin, Deutsche med. Wchnschr. **68**:157, 1942.

61. Brokaw, K. F.; Sedam, M. S., and Cassirer, A. M.: Influence of Diet on Physiologic Anemia of Infants, J. Pediat. **21**:769, 1942.

62. Marsh, A. G.; Leverton, R. M.; McMillan, T. G., and Underwood, G. R.: Absorption of Iron from Ferrous Sulfate with Observations on Hemoglobin Changes and Influence of Certain Intestinal Protozoa, Am. J. Digest. Dis. **10**:382, 1943.

absorbed from a supplement of ferrous sulfate containing 126 mg. of iron given daily for five to six weeks, whereas the remaining 17 were concerned with the excretion of iron after such a supplement had been discontinued. Under the conditions of the study the daily average absorption was slightly more than 50 per cent of the daily intake, regardless of whether the ingestion of ferrous sulfate was limited to one week or if it was given for several weeks. The average amount of iron retained by these subjects was 3.225 mg., but no significant change in the hemoglobin values was observed. Twenty-one of the subjects harbored either Endamoeba histolytica or other intestinal protozoa, and their rate of iron absorption was the same as that of noninfected subjects and was unaltered after the administration of a protozoacide. The average amount of iron absorbed daily by all the subjects was 76.79 mg. over a period of five to six weeks, a quantity equal to that reported in the literature for persons receiving by mouth the usual medicinal dose of iron, or about eight times the amount ingested by the subjects of this investigation. During the thirty days that followed a week of administration of an iron salt there was no evidence of excretion of any of the supplement. No indication was afforded by these observations that the body has any control over either absorption or excretion of iron.

The intake and excretion of iron of a 60 year old woman with hemolytic anemia who received 28 pints (13 liters) of blood over a fifteen week period was studied by McCance and Widdowson.[63] There was no evidence during the period of observation of excretion of any of the approximately 8 Gm. of iron contained in the transfused blood. The spleen, removed at operation, contained 0.32 Gm. of iron.

Less effect on the color and keeping qualities of bread is exerted by iron phytate than by other more soluble and more easily ionized iron salts. For this reason iron phytate has been extensively used in the fortification of flour, and the question of its availability to the human organism has therefore arisen. Moore, Minnich and Dubach[64] studied the absorption of iron when fed as the phytate by means of determinations of serum iron and found that iron phytate was much less readily absorbed from the intestinal tract than ferrous sulfate. When tested for its therapeutic efficacy in the treatment of patients with hypochromic anemia it was found that 1 Gm. of iron as the phytate had less effect on hemoglobin regeneration than approximately 0.3 Gm. of iron as ferrous sulfate. Calculations based on the recommendations of the National Research Council's Food and Nutrition Board with respect to the addition of iron to flour and on the observed absorption of iron when ingested as iron phytate indicate that the daily consumption of six to eight slices of bread fortified with iron phytate would probably lead to the absorption of only a fraction of a milligram of iron.

McCance, Edgecombe and Widdowson[65] determined the serum iron content of 9 normal subjects, of whom 4 were males and 5 females. The samples of blood were removed after test breakfasts composed of white bread, jam and iron salts. After such a breakfast there was a rise in the serum iron level, which, generally speaking, was greater after the ingestion of ferrous than of ferric salts. When sodium phytate was incorporated in the bread, other conditions being unchanged, the usual rise of the serum iron was not observed. It was therefore concluded, assuming that the rise in serum iron is proportional to the amount of iron absorbed, that sodium phytate interferes with the absorption of the metal. A similar but less regular effect was observed when disodium hydrogen phosphate was included in the bread. According to the authors, both ferrous and ferric phytate have been demonstrated to be less soluble than the corresponding phosphates at the reaction of the intestinal contents.

The relation of dietary calcium phosphorus and vitamin D to absorption and utilization of iron has been extensively studied by Fuhr and Steenbock.[66] They found that when rats were fed a synthetic ration containing a limited amount of iron in the form of ferric chloride and a quantity of calcium optimal for growth and calcification, slightly less hemoglobin was produced when the optimal amount of phosphorus was supplied as phytic acid than when it was given as a mixture of the mono and dipotassium phosphates. An excess of calcium in such a

63. McCance, R. A., and Widdowson, E. M.: Iron Excretion and Metabolism in Man, Nature, London **152**:326, 1943.

64. Moore, C. V.; Minnich, V., and Dubach, R.: Absorption and Therapeutic Efficacy of Iron Phytate, J. Am. Dietet. A. **19**:841, 1943.

65. McCance, R. A.; Edgecombe, C. N., and Widdowson, E. M.: Phytic Acid and Iron Absorption, Lancet **2**:126, 1943.

66. Fuhr, I., and Steenbock, H.: Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron: Effect of Phytic Acid on Availability of Iron, J. Biol. Chem. **147**:59, 1943; Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron: Effect of Vitamin D on Body Iron and Hemoglobin Production, ibid. **147**:65, 1943; Effect of Dietary Calcium, Phosphorus and Vitamin D on Utilization of Iron: The Relation of Rickets to Anemia, ibid. **147**:71, 1943.

diet reduced the formation of hemoglobin and the storage of iron. Administration of vitamin D improved the formation of hemoglobin and the storage of iron when the diet contained optimal amounts of calcium and phosphorus but not when an excess of calcium was provided. When the basal ration consisted of milk supplemented with copper and manganese a limited amount of iron supplied as ferric phytate produced 19 per cent less hemoglobin than an equal amount of iron in the form of ferric ammonium sulfate. Fuhr and Steenbock found that the addition of vitamin D to a synthetic ration optimal for growth with respect to its content of calcium and phosphorus and of known iron content led to an increase in hemoglobin and especially in the total amount of body iron. Although there was no effect on body weight following the administration of vitamin D, a marked increase in the weight of the liver was observed. Vitamin D apparently had no influence on the storage of copper. The authors found in rats that the presence of rickets produced by low dietary levels of calcium and phosphorus was not associated with a reduction in the amount of body iron or in the rate of hemoglobin synthesis.

Nakamura and Mitchell [67] compared the effect of ferric chloride with the effects of sodium iron pyrophosphate, reduced iron and ferric phytate in paired feeding experiments on anemic rats. Values for hemoglobin and for total retention of iron were determined, and their observations revealed that in terms of iron ingested reduced iron and sodium iron pyrophosphate were as effective as ferric chloride but that ferric phytate had only about one half the effect. Street [68] disagrees with these investigators with respect to sodium iron pyrophosphate. He found this compound only one half as effective as ferrous sulfate when fed to anemic rats either as an iron supplement or in the form of enriched bread.

The effect of honey in preventing or curing anemia of rats induced by a milk diet was observed by Haydock, Palmer and Tanquary.[69] The honey was added as a 20 per cent supplement to the milk, and it was found that the dark variety was much more effective than the light. The difference in the results obtained with the two types of honey may presumably be attributed to their varying content of iron and copper, although no determinations of these elements were made.

Theriault and Fellers [70] found that commercial quick freezing of foods increased slightly their content of available iron. Canning in glass had little or no effect on the total or available iron. Foods canned in tin showed changes in iron content which were fairly well correlated with the hydrogen iron concentration of the foods. There were either no changes or very slight gains in iron in the case of vegetables; considerable gains were observed in peaches attributable to their acidity, whereas half of the total and nearly all of the available iron of red sea perch, at a p_H of 6.9, were lost when the fish were packed in tin cans lined with zinc enamel. When iron was gained by food from cans the metal appeared to be almost 100 per cent available. Both the alpha, alpha-dipyridyl method and the rat bioassay method were employed in these investigations, and fairly good agreement between them was obtained.

Rats were fed riboflavin-deficient diets by Shukers and Day,[71] who observed development of leukopenia with relative and absolute decrease in lymphocytes and relative increase in neutrophils. Anemia was an inconstant finding and occurred in only a few of the rats toward the end of the experimental period. However, it was found that control animals suffering from inanition exhibited the same type of changes in the blood.

The effect of protein deficiency on the blood values of young rats was studied by Orten and Orten.[72] The diet of the experimental animals contained 3.5 per cent protein as lactalbumin, and the results were controlled by observations made on rats receiving 18.5 per cent lactalbumin and also by paired feeding studies in which the calories were kept constant but the differences in protein maintained. In the rats receiving the low protein diet mild hypochromic anemia developed, which could be prevented or cured by an adequate protein intake without changing the consumption of calories, minerals or vitamins. When the dietary protein was deficient the ingestion of a greater number of calories or of a larger amount of iron failed to exert a

67. Nakamura, F. I., and Mitchell, H. H.: Utilization for Hemoglobin Regeneration of Iron in Rats and in Enrichment of Flour and Bread, J. Nutrition **25**:39, 1943.

68. Street, H. R.: A Study of the Availability of the Iron in Enriched Bread, J. Nutrition **26**:187, 1943.

69. Haydock, M. H.; Palmer, L. S., and Tanquary, M. C.: Role of Honey in Prevention and Cure of Nutritional Anemia in Rats, J. Pediat. **21**:763, 1942.

70. Theriault, F. R., and Fellers, C. R.: Effect of Freezing and of Canning in Glass and in Tin on Available Iron Content of Foods, Food Research **7**: 503, 1942.

71. Shukers, C. F., and Day, P. L.: Effects of Inanition and Riboflavin Deficiency upon Blood Picture of Rat, J. Nutrition **25**:511, 1943.

72. Orten, A. U., and Orten, J. M.: The Role of Dietary Protein in Hemoglobin Formation, J. Nutrition **26**:21, 1943.

consistent beneficial effect on hemoglobin regeneration. The authors conclude that an adequate intake of dietary protein is essential for normal hemoglobin formation in the rat.

In confirmation of previously reported studies Smith, Curry and Hawfield [73] were able to produce hypochromic anemia in dogs by means of diets deficient in vitamin B_6, and they obtained improvement of the blood picture following the administration of this component of the B complex. However, they were unable to maintain normal hemoglobin values by the use of vitamin B_6 either alone or in combination with other known purified B vitamins. When brewers' yeast, in a concentration of 10 per cent, was incorporated in the basal diet the hemoglobin was maintained at levels between 18 and 20 Gm. per hundred cubic centimeters. This range is from 4 to 6 Gm. above the usually recorded normal value for the dog.

The regeneration of hemoglobin and plasma proteins by dogs depleted in both respects was studied by Robscheit-Robbins, Miller and Whipple.[74] They found that hemoglobin production was always favored, even when protein was supplied by the intravenous injection of dog plasma. A mixture of crystalline amino acids (Rose) was the most efficacious of all materials tested in regeneration of hemoglobin. The production ratio of plasma protein to hemoglobin ranged from 30 to 60 per cent and the ratio was increased when cystine replaced methionine in the diet. The authors point out that hemoglobin protein is normally about three times as great in amount as plasma protein, and this may account for the greater production of hemoglobin with all materials tested. They conclude that plasma, serum digests, casein digests, hemoglobin and hemoglobin digests and amino acids all appear to contribute efficiently to the body protein pool.

Hahn and his associates [75] attempt to explain why iron is absorbed from the intestine in larger quantities in the presence of iron deficiency anemia. Their data were secured by means of determination of the radioactive iron content of the plasma of dogs. Acute anemia, they found, is not followed by increased absorption of iron. Before the latter can occur there must be depletion of the stores of the metal, which requires about seven days. Iron administered orally in ordinary doses caused some degree of mucosal "block" if it was given from one to six hours before the ingestion of radioactive iron. Injection of iron salts by vein some days before the oral administration of radioactive iron did not prevent absorption. Many variables may affect the absorption of iron, such as temperature and degree of peristalsis, and absorption curves of plasma radioactive iron vary greatly. Gastric, duodenal and jejunal pouches all showed extremely active absorption of iron. The authors suggest an "acceptor," or valve, mechanism in the gastrointestinal mucosa, dependent on the cell content of iron as compared with that of the plasma on the one side and with that of the intestinal contents on the other. It is believed that iron in the plasma does not pass out through the mucosa because of its attachment to globulin. The destruction of the mucosa appears to be a matter of days, whereas saturation may occur in one to two hours. The absorption and release of iron by the mucosa are believed to be a part of the complex protein metabolism of the cell.

Spector and his associates [76] fed dogs a purified diet supplemented with crystalline B vitamins except for riboflavin. The food consumption was poor and irregular, and evidences of deficiency were present in all the animals. Mild anemia developed, and after bleeding the anemia became more severe than would have been anticipated from the amount of blood withdrawn. The blood values could not be restored to normal unless riboflavin was added to the diet. The anemia associated with riboflavin deficiency was microcytic and hypochromic unless the dogs were bled, when it became normocytic and hypochromic.

The production of polycythemia in rats by means of cobalt was confirmed by Dorrance and his associates,[77] who observed an elevation in average hemoglobin value from 15.6 to 20.4 Gm. per hundred cubic centimeters after five to six weeks of cobalt supplementation. They were able to demonstrate an increased work performance in such polycythemic rats, but a still greater increase was noted when the administration of cobalt was discontinued and before the blood values had fallen. The effect was not due apparently to cardiac hypertrophy, since differences

73. Smith, S. G.; Curry, R., and Hawfield, H.: Vitamin B_6 Deficiency Anemia in the Dog, Science **98**: 520, 1943.

74. Robscheit-Robbins, F. S.; Miller, L. L., and Whipple, G. H.: Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma Hemoglobin, and Digests of Serum, Hemoglobin, and Casein, J. Exper. Med. **77**:375, 1943.

75. Hahn, P. F., and others: Radioactive Iron Absorption by Gastro-Intestinal Tract: Influence of Anemia, Anoxia, and Antecedent Feeding Distribution in Growing Dogs, J. Exper. Med. **78**:169, 1943.

76. Spector, H.; Maass, A. R.; Michaud, L.; Elvehjem, C. A., and Hart, E. B.: The Role of Riboflavin in Blood Regeneration, J. Biol. Chem. **150**:75, 1943.

77. Dorrance, S. S., and others: Effect of Cobalt on Work Performance Under Conditions of Anoxia, Am. J. Physiol. **139**:399, 1943.

in the weights of the hearts of the experimental animals were not observed. There was erythrohyperplasia of the bone marrow associated with polycythemia and myeloid metaplasia in the spleen. The latter organ was enlarged, apparently as a result of vascular congestion in rats which had been subjected to work performance tests during administration of cobalt and for six weeks after its discontinuation.

Hahn and his associates [78] studied the formation and storage of ferritin in the animal body. They found that iron in the form of ferric ammonium citrate when administered by vein to the dog is readily converted into ferritin iron in the liver. Iron derived from hemoglobin of the circulating red blood cells after the destruction of the cells by acetylphenylhydrazine is in part at least converted to ferritin iron in the liver and spleen. Their observations indicated that the body is able to convert injected ferric iron of the form containing 5 unpaired electrons to ferric iron of the form possessing 3 unpaired electrons, a structure which is characteristic of ferritin. Further support is given to the view that ferritin iron acts in the capacity of storage iron in the animal body.

Sachs and his co-workers [79] review the work previously reported by them and by other authors on the copper and iron content of whole blood and serum, studies of absorption of iron and copper and on the role of these metals in anemia. They state: "We have never found a copper deficiency in analyses of the blood that we have made and we do not feel that added copper is needed in the treatment of iron deficiency anemia."

ANEMIA IN PREGNANCY

The blood values of five groups of subjects were studied by Botella Llusia and Echarri [80]: (1) nonpregnant women who had received a good diet; (2) healthy pregnant women whose diets had been good; (3) healthy pregnant women whose diets had been poor; (4) pregnant women with toxemia, and (5) women seen for the first time after delivery. The pregnant patients were examined at the conclusion of gestation. The authors found many persons with true anemia in the group receiving a poor diet and in the toxemic group. In women with anemia not associated with toxemia the causative factor appeared to be a deficiency of iron, whereas in the toxemic patients other mechanisms appeared to be operative and the blood picture often included macrocytosis. The incidence of anemia after confinement appeared to be related to the degree of anemia during pregnancy and to the amount of loss of blood during parturition, except that in cases of puerperal sepsis severe anemia was almost always present.

The nutritional status and hematologic values of 484 pregnant women residing in a rural area were evaluated by Bethell, Blecha and Van Sant.[81] The incidence of anemia in the group was 25.4 per cent, and a positive correlation was established between the occurrence of hypochromic anemia and dietary deficiency of iron, and between macrocytic anemia and an inadequate intake of protein. Merchante [82] studied the changes in the blood during pregnancy in 46 women and found that after a transient slight rise of hemoglobin in the second month there was a rapid decline in the third month, with continued gradual reduction up to the eighth month, followed by a slight rise in the ninth month. The average hemoglobin value in the first month was 12.55 Gm. per hundred cubic centimeters, in the second it was about 13 Gm., and in the ninth it fell to 11.45 Gm. The erythrocyte count declined progressively from an initial level of 4,360,000 per cubic millimeter to one of 3,570,000 at the end of pregnancy, with a parallel fall in the packed cell volume percentage from 42.4 to 39.0.

One hundred and seven cases of anemia in pregnancy observed in Calcutta, India, were studied by Bagchi.[83] In 3 of these the anemia was attributable to parasitic disease. The remainder included 10 cases of hypochromic anemia and 94 cases of orthochromic macrocytic anemia. The highest incidence of severe anemia occurred in women who were in their first pregnancy and who were between 21 and 30 years of age. The largest number of patients were seen in the eighth month of gestation, and there appeared to be a greater frequency of anemia in the months of September through January inclusive. Patients with anemia were predominantly in a low economic class. Treatment consisted of administration of liver extract and iron salts and intramuscular injections of whole blood.

78. Hahn, P. F.; Granick, S.; Bale, W. F., and Michaelis, L.: Ferritin Conversion of Inorganic and Hemoglobin Iron into Ferritin Iron in the Animal Body: Storage Function of Ferritin Iron as Shown by Radioactive and Magnetic Measurements, J. Biol. Chem. **150**:407, 1943.

79. Sachs, A.; Levine, V. E.; Hill, F. C., and Hughes, R.: Copper and Iron in Human Blood, Arch. Int. Med. **71**:489 (April) 1943.

80. Botella Llusia, J., and Echarri, M.: Estudios sobre las verdaderas y falsas anemias en el embarazo parto y puerperio, Rev. clín. españ. **7**:262, 1942.

81. Bethell, F. H.; Blecha, E., and Van Sant, J. H.: Nutritional Inadequacies in Pregnancy Correlated with Incidence of Anemia, J. Am. Dietet. A. **19**:165, 1943.

82. Merchante, F. R.: Contribución al estudio de la sangre durante el embarazo, Semana méd. **2**:1273, 1942.

83. Bagchi, S.: Anemia of Pregnancy, J. Indian M. A. **12**:199, 1943.

Transfusions were rarely required. Evans [84] reports determinations of hemoglobin and of erythrocyte made for 117 women during pregnancy. Administration of ferrous sulfate in a dosage of 1 Gm. daily is advocated in all cases in which the hemoglobin declines to a level of about 10 Gm. per hundred cubic centimeters or less.

A case of microcytic anemia in pregnancy associated with a megaloblastic reaction of the marrow in a patient who had continuous diarrhea throughout the nine months of gestation is reported by Foy and Kondi.[85] Alessandri and Etcheverry [86] report 2 cases of macrocytic anemia in pregnancy and discuss the prevention of such anemia by means of a diet containing meat, eggs, whole grain cereals and brewers' yeast. Fullerton [87] describes the cases of 3 women with macrocytic anemia observed either in the latter weeks of pregnancy or in the puerperium who failed to respond satisfactorily to parenteral administration of liver extract, but improved rapidly when mixed therapy including whole liver was instituted. A case of aplastic anemia in the latter months of pregnancy terminating fatally is reported by Düpmann.[88]

HEMOLYTIC ANEMIAS AND ERYTHROBLASTIC ANEMIAS

The hemolytic syndromes are discussed by Davis,[89] who presents the following classification of these disorders grouped according to known or supposed cause: (1) abnormalities of the red cells, such as familial acholuric jaundice, sickle cell anemia and nocturnal hemoglobinuria; (2) hemolysins, occurring in certain transfusion reactions, in reactions due to Rh isoimmunization and in bacterial infections; (3) parasitic infection of the red cells, as found in malaria and in oroya fever; (4) poisons exerting a lytic or other action on the red cells, including lead, phenylhydrazine and arsenicals; (5) hypersensitivity to drugs and other agents, such as the sulfonamide compounds and the Fava bean; (6) cause unknown but associated with predisposing factors, such as blackwater fever and march hemoglobinuria; (7) cause completely unknown, as with acute hemolytic anemia (Lederer) and familial erythroblastic anemia (Cooley's anemia).

Acquired Types of Hemolytic Anemia.—Dameshek [90] outlines the management of acute hemolytic anemia and the hemolytic crisis on the basis of his experience with 25 cases, each of which is presented briefly. He advocates transfusion to combat the severe anemia as the first step in therapy but warns against the too free use of blood. The purpose of transfusion is the restoration of the red cells to a safe level, as a specific therapeutic measure, which may in some cases terminate the acute hemolytic process and thereby render splenectomy unnecessary. Splenectomy was performed on 23 of the 25 patients reported, with recovery in 10 of the 18 with the acquired form of the disease and beneficial results in 4 of the 5 with familial hemolytic anemia. Laboratory methods helpful in studying hemolytic anemia are given in some detail. Tests for cold and warm agglutinins as well as for autohemolysins and isohemolysins are recommended in each instance. The Landsteiner-Levine test tube technic for cross matching blood, in which the blood serum suspension is warmed at 37 C, is considered invaluable for the elimination of false negative reactions in the presence of warm isohemolysins or agglutinins, such as the Rh factor. The blood type of the donor should conform to that of the recipient, for group O plasma containing isoagglutinins a and b might result in a severe hemolytic transfusion reaction in the presence of a severe anemia with spherocytosis. Fresh rather than stored blood is recommended, since the fresh cells may be better able to withstand the action of a circulating lysin.

Since 1916 Mason [91] has observed 12 cases of acquired hemolytic anemia, including examples of the acute and the chronic form, the latter characterized by a variable rate of hemolysis. Credit for the first report of acute hemolytic anemia is given to MacKintosh and Cleland, and Widal and others are cited as having published later accurate descriptions. The author suggests that the term acquired hemolytic icterus be used, with the qualifying adjectives of acute or chronic. The acute form of the disease is identical with that described by Lederer. The onset in children is abrupt, with chills and fever, whereas in adults the hemolytic process is more insidious at the start. Pallor, jaundice and fever

84. Evans, E. G.: Anemia in Pregnancy, Illinois M. J. **84**:317, 1943.

85. Foy, H., and Kondi, A.: Ehrlich's Megaloblasts Associated with Low Mean Corpuscular Volume and Red Cell Diameter, Lancet **2**:505, 1943.

86. Alessandri, R. H., and Etcheverry, R.: Dos observaciones clínicas de anemia perniciosa del embarazo, Rev. méd. de Chile **71**:261, 1943.

87. Fullerton, H. W.: Macrocytic Anaemia of Pregnancy and Puerperium, Brit. M. J. **1**:158, 1943.

88. Düpmann, P.: Normacytäre, aplastische Anämie am Ende der Gravidität, Zentralbl. f. Gynäk. **67**:410, 1943.

89. Davis, L. J.: Haemolytic Anaemias, Edinburgh M. J. **50**:589, 1943.

90. Dameshek, W.: The Management of Acute Hemolytic Anemia and the Hemolytic Crisis, Clinics **2**:118, 1943.

91. Mason, V. R.: Acquired Hemolytic Anemia, Arch. Int. Med. **72**:471 (Oct.) 1943; The Acute Hemolytic Anemias of Unknown Etiology, Tr. A. Am. Physicians **57**:234, 1942.

are constantly present, the erythrocyte count frequently being less than 1,000,000 per cubic millimeter. Other hematologic features include macrocytes containing normal or only slightly less than normal amounts of hemoglobin, numerous microspherocytes, frequent nucleated red cells, poikilocytes, diffuse and punctate basophilic erythrocytes and reticulocytosis, the count perhaps exceeding 80 per cent. Leukocytosis with a pronounced increase in young granulocytes is a usual finding. Both the platelet count and the resistance of erythrocytes in hypotonic solutions of sodium chloride are generally normal, but extreme osmotic fragility is occasionally encountered. In 3 of the cases hemolysis began with 0.85 to 0.80 per cent sodium chloride and was not complete until 0.26 to 0.28 per cent concentrations were reached. In a fourth case the erythrocytes began to undergo hemolysis with 0.84 per cent sodium chloride and the process was complete with 0.34 per cent. Mason remarks that this unusually wide range of resistance is seldom seen in other conditions. Hemolysins could not be demonstrated in the serum in any case studied, although autoagglutination was encountered in 4. The outcome of the acquired form of the disease is extremely variable. Spontaneous remissions and cures by transfusion or splenectomy are observed, while a chronic course interrupted by hemolytic crises may ensue. Splenectomy may cure or improve the disorder at any stage, and in a serious hemolytic crisis it may be a life-saving procedure. The differential diagnosis between the acute acquired and the congenital form of hemolytic anemia depends largely on morphologic study of the blood films and on a careful family history with examination of the blood of relatives. Increased fragility in hypotonic solution is not proof that the disease is congenital icterus, as this is observed in about half of the cases of the acquired form. The hemolytic crises occurring in congenital hemolytic icterus are rarely as severe as those which develop in the course of acquired hemolytic processes.

Poncher, Weir and Davidsohn [92] report an instance of acute hemolytic anemia in a 4½ year old girl with fatal termination despite splenectomy. An atypical cold agglutinin was demonstrated, and because of many allergic manifestations unsuccessful attempts were made to alter the resistance of the erythrocytes to hypotonic solution of sodium chloride by the addition in vitro of various allergens to which the patient was reactive. Pepper and Austin [93] report an interesting follow-up examination of a patient who had had the spleen removed for hemolytic anemia twenty-eight years before. Howell-Jolly bodies were present in the erythrocytes, which, so far as is known, represents the longest reported persistence of these bodies after splenectomy. Kracke and Hoffman [94] report the case of a 32 year old white woman with chronic hemolytic anemia accompanied by autoagglutination and hyperglobulinemia. The autoagglutination observed was not of the type which may be associated with hyperglobulinemia. During the terminal phase of the patient's illness 10 Gm. of acacia in 6 per cent solution was given intravenously, without any observed effect on the hemolytic process, although the total serum protein decreased from 10.66 to 7.75 Gm. per hundred cubic centimeters of whole blood, the reduction being relatively greater in the globulin fraction. Splenectomy was likewise without avail in arresting the hemolytic process. The serologic reaction for syphilis, previously positive, became negative after the operation. A case of acute and likewise fatal hemolytic anemia associated with autoagglutination in a 32 year old woman is reported by Evans.[95] Autoagglutination was demonstrated at 37 C., and the phenomenon persisted after splenectomy.

Wilson and Mangun [96] encountered 3 cases of acute hemolytic anemia with hemoglobinuria in workers in the fertilizer industry. These persons were at work in the hold of a ship carrying fish scrap, which is used as a source of ammonia nitrogen. The etiologic agent responsible for the hemolytic process was found to be arsine gas. An active hemolysin was reportedly isolated from the blood of one patient and from the urine of another.

Eads and Kash [97] report a case of acute hemolytic anemia, jaundice and hemoglobinuria due to ingestion of the Fava bean. It is pointed out that this disease should be of particular interest to the military forces engaged in the Mediter-

92. Poncher, H. G.; Weir, H. F., and Davidsohn, L.: Observations on Hemolysis in Acute Hemolytic Anemia: A Case Report, J. Pediat. **22**:387, 1943.

93. Pepper, O. H. P., and Austin, J. H.: A Twenty-Eight Year Follow-Up on a Splenectomy for Hemolytic Anemia: Persistence of Howell-Jolly Bodies, J. A. M. A. **122**:870 (July 24) 1943.

94. Kracke, R. R., and Hoffman, B. J.: Chronic Hemolytic Anemia with Autoagglutination and Hyperglobulinemia: Report of a Fatal Case, Ann. Int. Med. **19**:673, 1943.

95. Evans, R. S.: Acute Hemolytic Anemia with Autoagglutination: A Case Report, Stanford M. Bull. **1**:178, 1943.

96. Wilson, R., Jr., and Mangun, G. H.: Acute Hemolytic Anemia in Fertilizer Workers: A New Industrial Hazard, South. M. J. **36**:212, 1943.

97. Eads, J. T., and Kash, R. M.: Favism: Report of a Case, U. S. Nav. M. Bull. **41**:1720, 1943.

ranean area, where the Fava bean serves as an important article of diet.

A heretofore undescribed hemolytic anemia occurring in young swine is reported by Robb.[98] A rapid sedimentation rate, agglutination of erythrocytes and the presence of normoblasts in the peripheral blood are described.

Hemolytic Anemia Produced by Sulfanilamide and Derivatives.—Acute hemolytic anemia has been reported following the use of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. An acute fulminating hemolytic syndrome which developed over a forty-eight hour period after the administration of 12 Gm. of sulfanilamide is reported by Murley.[99] The patient was a 31 year old man who was receiving treatment for multiple venereal sores. Hemoglobinuria was present before death. At necropsy early acute fat necrosis was present in the liver and marked hemosiderosis was evident in the spleen, which was engorged and showed areas of extensive destruction of erythrocytes. Partial necrosis of the cells lining the convoluted tubules was present in the kidney. Russell[100] reports a case of acute hemolytic anemia with a leukemoid reaction that developed after 8 Gm. of sulfanilamide was placed in the abdominal cavity at the time of an exploratory operation and removal of a normal appendix. The leukocyte count reached 110,000 per cubic millimeter. Manson-Bahr[101] observed a similar condition following oral ingestion of 25 Gm. of sulfanilamide during a four day period. Both of these patients and another observed by Eglitzky,[102] who also received sulfanilamide, recovered spontaneously. Jones[103] reports a case of hemolytic anemia with macrocytosis in which the anemia developed eleven days after the institution of sulfapyridine therapy and three days after its discontinuance. A total of 24 Gm. had been given. An oral test dose of 1 Gm. of sulfapyridine given to the patient caused a fall in the hemoglobin level from 80 to 66 per cent and in the hematocrit value from 43 to 34.5 per cent. In vitro incubation of the patient's cells with sulfapyridine failed to cause hemolysis. Boyer[104] observed a case of acute hemolytic anemia after the administration of 16 Gm. of sulfapyridine in a four day period. Dowling and Lepper[105] from observations of a large series of patients treated with three of the sulfanilamide derivatives found that the incidence of hematologic complications, except for acute hemolytic anemia, was not significantly different. The group comprised 568 persons who had received sulfapyridine, 321 who had been given sulfathiazole and 660 who had been treated with sulfadiazine. Only 1 case each of hemolytic anemia following sulfathiazole and sulfadiazine therapy were observed. Seven patients (1.4 per cent) had hemolytic anemia after receiving sulfapyridine. This complication occurred between the second and the seventh day after the onset of therapy. Leukopenia, with a count of less than 4,000 cells per cubic millimeter, occurred in 1.2 per cent of the patients treated with sulfapyridine and sulfathiazole and in 0.9 per cent of those given sulfadiazine. The incidence of hemolytic anemia produced in mice by sulfamerazine, sulfadiazine and sulfapyridine was investigated by Latven and Welch.[106] The drugs were incorporated into the stock ration, and the blood level associated with a 50 per cent incidence of anemia was determined for each drug. The values obtained were 2.8 mg. per hundred cubic centimeters for sulfapyridine, 33 mg. for sulfadiazine and 31 mg. for sulfamerazine. The concentrations of the three drugs within the erythrocytes at these blood levels were respectively 2.5 mg., 26 mg. and 23 mg. per hundred cubic centimeters. The toxic effects of promin (sodium P,-P'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) on the erythrocytes of guinea pigs was studied by Higgins.[107] A direct action on the erythrocytes was demonstrated, with hemolytic anemia, splenomegaly and reticulocytosis developing in the experimental animal.

98. Robb, A. D.: Letero-Anemia in Growing Swine, Vet. Med. **38**:271, 1943.

99. Murley, R. S.: Acute Fulminating Haemolytic Syndrome, Fat Necrosis of the Liver and Acute Necrotizing Nephrosis Following Sulphanilamide Therapy, J. Roy. Army M. Corps **80**:182, 1943.

100. Russell, H. K.: Acute Hemolytic Anemia Associated with Leukemoid Reaction Following Administration of Sulfanilamide, U. S. Nav. M. Bull. **41**:1399, 1943.

101. Manson-Bahr, P. E. C.: Case of Acute Haemolytic Anaemia with a Leukaemoid Reaction Following the Administration of Sulphanilamide (M. & B. 125), East African M. J. **20**:86, 1943.

102. Eglitzky, B. C.: A Case of Acute Haemolytic Anaemia Caused by Sulphanilamide, M. J. Australia **1**:536, 1943.

103. Jones, E. I.: Haemolytic Anaemia Due to Sulfapyridine, Lancet **1**:201, 1943.

104. Boyer, N. H.: Acute Hemolytic Anemia Following Sulfadiazine: Report of a Case, New England J. Med. **228**:566, 1943.

105. Dowling, H. F., and Lepper, M. H.: Toxic Reactions Following Therapy with Sulfapyridine, Sulfathiazole and Sulfadiazine, J. A. M. A. **121**:1190 (April 10) 1943.

106. Latven, A. R., and Welch, A. D.: The Incidence of Hemolytic Anemia in Mice Fed Diets Containing Sulfamerazine, Sulfadiazine, or Sulfapyridine, Am. J. M. Sc. **206**:805, 1943.

107. Higgins, G. M.: Toxic Effects of Promin (Sodium P,P'-Diamiodiphenylsulfone—N,N'-Didextrose Sulfonate) on the Erythrocytes of Guinea Pigs, Am. J. M. Sc. **205**:834, 1943.

Congenital Hemolytic Jaundice.—Dacie and Mollison [108] report the duration of survival of transfused erythrocytes given to 6 patients with congenital hemolytic jaundice. The Ashby technic of differential agglutination was applied to the recipients' blood after transfusion. Group O blood was given to 5 patients belonging to group A, and the remaining patient, whose blood was of type 0, was tested with anti-M serum. The total survival time of the transfused erythrocytes in 5 of 6 patients was considered normal and fell at about one hundred days. In the sixth patient the transfused cells had disappeared at the end of sixty days. These observations are cited as evidence that the formation of faulty erythrocytes with a tendency to hemolysis is the fundamental defect in the disease, in contradistinction to spherocytosis resulting from the action of a circulating hemolysin. Further support to this view is given by the observation that cells of patients with familial hemolytic jaundice survived only fourteen days after transfusion into a normal person. This procedure was repeated some years after splenectomy with cells from the same patient, with a similar complete destruction of the transfused cells noted at the end of nineteen days. Unless it is hypothesized that the hemolysin is specific for the patient's erythrocytes, it is difficult to reconcile these observations with the view that hemolysins are the etiologic factor in this disease. Lowe [109] followed the blood values and the excretion of stercobilin and urobilin of a 15 year old white boy suffering with congenital hemolytic jaundice in periods of clinical crisis, after repeated transfusions and before and after splenectomy. The crises occurred without any significant alteration in the rate of destruction of blood but were accompanied by evidence of diminished hepatic function. A sudden increase in urinary urobilin and blood bilirubin with a change in the van den Bergh reaction from the indirect to a progressively stronger direct type, enlargement and tenderness of the liver and diminished hippuric acid synthesis led to the conclusion that crises may be associated primarily with changes in hepatic function. These abnormalities were rapidly reversed without the institution of specific therapeutic measures. Repeated transfusions initiated a rapid increase in excretion of pigment. Splenectomy was followed by clinical cure, with subsequent normal blood values and rate of pigment excretion. Heimburg and Reuter [110] report a fatal crisis occurring ten months after splenectomy in a patient with familial hemolytic jaundice. Wiedemann [111] observed normal resistance of erythrocytes in hypotonic solution of sodium chloride in all of several members of one family reportedly suffering from familial hemolytic anemia. A similar situation is reported by Hudock and Patterson [112] in 1 parent and in 2 sisters who were seen in hemolytic crisis. An effort to demonstrate hemolysins proved futile in all 3 instances. Dacie [113] studied 24 patients with familial hemolytic anemia with particular reference to changes in the erythrocyte fragility produced by splenectomy. When the observations were expressed as the percentage of hemolysis occurring at each level of sodium chloride concentration, three types of curves resulted. A normal curve was encountered for 5 patients; 12 had a "tailed" curve, hemolysis being met with in concentrations between 0.76 and 0.58 per cent sodium chloride, and 6 had a "diagonal" curve. Splenectomy was performed on 12 patients, with subsequent increased resistance to hypotonic salt solutions in 11 cases and decreased resistance in 1. Pathologic study of the spleens in these cases revealed congestion as the only consistent abnormality. It is this investigator's opinion that the clinical and experimental evidence is such that the possibility of an abnormal hemolytic agent or metabolite cannot be ignored as an etiologic factor in this disease. The inheritance and linkage of the trait responsible for congenital hemolytic anemia were studied in 183 members of 26 families by Race.[114] The expected ratio, according to the mendelian law, of one normal sibling for each affected member was not found. This might be explained by the higher fetal and infant mortality rate in the jaundiced branches of the families. There was no evidence for the linkage of the responsible trait with sex, blood groups and taste inheritance.

108. Dacie, J. V., and Mollison, P. L.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anaemia (Acholuric Jaundice), Lancet **1**:500, 1943.

109. Lowe, R. C.: Study of Hemoglobin Metabolism and Hematology in Case of Congenital Hemolytic Jaundice During (A) Clinical Crisis, (B) Repeated Transfusions and (C) Before and After Splenectomy, Am. J. M. Sc. **206**:347, 1943.

110. Heimburg, J., and Reuter, V. H.: Fatal Hemolytic Crisis After Splenectomy in Hemolytic (Familial) Icterus, Ztschr. f. Kinderh. **63**:618, 1942.

111. Wiedemann, H. R.: Familiärer hämolytischer Ikterus und osmotische Hämolyse, Ztschr. f. Kinderh. **63**:501, 1942.

112. Hudock, E. B., and Patterson, S. M.: Congenital Hemolytic Anemia; Congenital or Familial Hemolytic Jaundice, Clinics **1**:1021, 1943.

113. Dacie, J. V.: Familial Haemolytic Anaemia (Acholuric Jaundice) with Particular Reference to Changes in Fragility Produced by Splenectomy, Quart. J. Med. **12**:1, 1943.

114. Race, R. R.: On the Inheritance and Linkage Relations of Acholuric Jaundice, Ann. Eugenics **11**: 365, 1942.

A similar failure resulted in an attempt to link this disorder with those traits whose inheritance is less certain, such as color of the eyes and attachment of the lobes of the ears. The blood factors investigated with reference to possible linkage included blood groups A_1, A_2, B, M and N and the secretion of factors A, B and O. The frequently reported occurrence of developmental abnormalities in this disorder are, in the opinion of the author, merely accidental. No reason was afforded by this study to change the opinion that congenital hemolytic jaundice is inherited as a dominant mendelian character.

Erythroblastosis Fetalis and the Rh Factor.—During the past year additional information has been acquired concerning the significance of the Rh factor in the causation of erythroblastosis fetalis and of hemolytic transfusion reactions.

The importance of the Rh factor in erythroblastosis fetalis is confirmed by Potter and his associates,[115] who examined 60 mothers giving birth to babies with the disease. All but 6 of the mothers were found to have Rh-negative blood and all but 6 of the 59 infants and fetuses to have Rh-positive blood. Three of the 6 infants born to mothers with Rh-positive blood were macerated, and the high infant mortality of the disease is emphasized when it is stated that the offspring of 55 of these mothers were examined at necropsy. Eighty-one mothers whose pregnancies ended in abortion or stillbirth or whose infants died shortly after birth from a cause other than erythroblastosis were examined, and only 25 per cent were found to have Rh-negative blood. In contrast, of the mothers who had children exhibiting definite evidence of the diease, 90 per cent had Rh-negative blood. Race and his associates[116] report on 50 families in which a child with erythroblastosis fetalis was born and found all but 6 of the mothers to have Rh-negative blood. Of the first children of the 44 mothers with Rh-negative blood, 38 were unaffected, 1 suffered from the disease and 5 were stillborn or victims of miscarriage; but from the second birth onward, a steady increase in the ratio of affected children occurred. In the 50 families studied, with but 1 exception, no mother who once produced an erythroblastotic baby subsequently delivered a normal child. Three quarters of the children affected were born dead or died within one week of life.

115. Potter, E. L.; Davidsohn, I., and Crunden, A. B.: The Importance of the Rh Blood Factor in Erythroblastosis, Am. J. Obst. & Gynec. **45**:254, 1943.

116. Race, R. R.; Taylor, G. L.; Cappell, D. F., and McFarlane, M. N.: The Rh Factor and Erythroblastosis Foetalis: An Investigation of Fifty Families, Brit. M. J. **2**:289, 1943.

The literature dealing with erythroblastic anemia is concisely reviewed by Flynn.[117] Eighty-six references are listed. A case is reported by the author in which the roentgenologic findings are of interest. The skull of the infant showed radial arrangement of bone spicules in the calvarium and unusually prominent trabeculae connecting the inner and outer tables. Generalized osteoporosis of the long bones and expansion of the metacarpal and phalangeal medullary cavities were evident. Levine[118] discusses serologic factors as possible causes of spontaneous abortions and gives thirty-nine references in a review of the Rh factor. Rothman and Hopkins[119] feel that the high mortality rate of erythroblastosis fetalis is not due entirely to the severity of the disease process or to transfusion of incompatible blood but that in at least a fair number of cases intrauterine asphyxia occurs. This suggestion is based on the personal observation of death with manifestations of asphyxia in 5 of 8 infants with the disease. When a history is obtained from a mother of a previous birth of an erythroblastotic infant certain prophylactic points are emphasized. Analgesia and inhalation anesthesia are contraindicated as they tend to increase intrauterine asphyxia. The most rapid means of delivery is imperative, and the justification for cesarean section becomes absolute.

Most writers agree that prompt transfusion is the only therapy of value for erythroblastosis fetalis. The procedures to be followed are critically discussed by Wiener and Wexler.[120] Rh-negative blood from group O donors, preferably with weak anti-A and anti-B isoagglutinins in the serum, is the blood of choice. Ten cubic centimeters per pound (22 cc. per Kg.) of body weight given intravenously at once and again in twenty-four hours and as often thereafter as necessary is recommended. Whole maternal blood is, of course, to be avoided, as additional iso-antibodies may be transferred to the infant. The father's blood cells and cells from other donors with Rh-positive blood are subject to attack by the anti-Rh antibodies present in the infant and hence cannot be used. In practice, Rh-negative, group O blood is widely used, although theoretically the donor should belong to the same group as the infant. The relative

117. Flynn, J. M.: Erythroblastic Anaemia with a Review of the Literature, Brit. J. Radiol. **16**:157, 1943.

118. Levine, P.: Serological Factors as Possible Cause of Spontaneous Abortions, J. Hered. **34**:71, 1943.

119. Rothman, P. E., and Hopkins, H.: The Relationship of Erythroblastosis Fetalis to Intrauterine Asphyxia, Am. J. Obst. & Gynec. **45**:291, 1943.

120. Wiener, A. S., and Wexler, I. B.: Transfusion Therapy of Acute Hemolytic Anemia of the Newborn, Am. J. Clin. Path. **13**:393, 1943.

insensitivity of the infant's red cells to the alpha and beta agglutinins, however, makes this procedure safe. The use of Rh-negative blood of the same group as that of the mother is the best procedure of all, for in such a circumstance if the Rh factor did not prove to be the responsible factor the washed erythrocytes of the mother could be used subsequently without untoward reaction. In the occasional instance in which an infant with acute hemolytic anemia is born to a mother with Rh-positive blood the transfusion of washed cells of the mother suspended in saline solution is also advocated. When Rh-negative blood has failed to produce the expected improvement, multiple sensitization involving unknown factors is a possibility, and here, too, the mother's cells, insensitive to iso-antibodies, offer a therapeutic tool.

Mollison [121] compared the survival rate of erythrocytes by differential agglutination with M and N antiserums when affected infants were given transfusions of Rh-positive and of Rh-negative blood. In all but exceptional instances, Rh-positive cells were found to disappear within ten days after transfusion into infants under 2 weeks of age. Rh-negative cells were seen to survive for eighty days or longer in 19 of 20 recipients. After the children reached 2 weeks of age or more, the survival of Rh-positive cells increased progressively, and in 2 of 4 cases it approximated the life cycle observed with Rh-negative erythrocytes. The survival rate of cells given to normal infants was approximately the same as noted in affected children given Rh-negative blood. Gimson [122] observed 18 consecutive infants who required only two transfusions at the most of Rh-negative blood to bring the blood values to normal. Lloyd [123] feels that when anti-Rh serum is not available for typing donors it is preferable, if a transfusion is urgently needed, to use maternal blood rather than to select a donor at random, whose blood would probably be Rh-positive. The presence of anti-Rh agglutinins in the mother's serum is recognized as a contraindication.

Gallagher, Danis and Jones [124] noted "severe or moderate jaundice" in 9 infants born to mothers with Rh-positive blood and feel that the diagnosis of erythroblastosis is not improved by the determination of the Rh factor. In 8 other infants with erythroblastosis, however, the expected Rh distribution between mother and child was found.

Kariher and Spindler [125] suggest that the term erythroblastosis be dropped, as it implies that all infants suffering from icterus gravis, fetal hydrops and hemolytic anemia have erythroblasts in increased numbers in the blood. As this is not always true, as illustrated by 2 cases of their own, the term "hemolytic disease of the newborn" is advanced as a more descriptive classification, since hemolysis is the fundamental reaction.

Dameshek, Greenwalt and Tat [126] present further evidence that erythroblastosis fetalis is primarily an acute hemolytic anemia. The quantitative excretion of the breakdown products of hemoglobin of 3 infants with the disease was studied and compared with that of normal newborn infants. The hemolytic index, which expresses the number of milligrams of bile pigment derived from each 100 Gm. of circulating hemoglobin, was approximately 2.5 times greater in the case of the 3 affected infants than the highest value for the normal infants. The values obtained for the erythroblastotic children compared in severity to the indexes observed in the hemolytic crises of hereditary spherocytic jaundice and acute acquired hemolytic anemia. The evidence of increased hemolysis in this disease includes acute onset of anemia, jaundice and bilirubinemia, increased fecal bilirubin and an increased hemolytic index. Indirect evidence is afforded by a biphasic Price-Jones curve, reticulocytosis, erythrocytosis, leukocytosis with a leukemoid reaction and myeloid metaplasia of the spleen and liver. The normomacrocytic anemia, or what is termed "pseudomacrocytic" by the authors, is likewise cited as indirect evidence of a hemolytic process, the apparent macrocytosis being due to the large numbers of reticulocytes present.

Reisner [127] constructed Price-Jones curves in 12 cases of fetal hydrops and in an equal number of cases of icterus gravis. In all but 1 case a characteristic bimodal curve, consisting of normocytic and macrocytic peaks or with two macro-

121. Mollison, P. L.: The Survival of Transfused Erythrocytes in Haemolytic Disease of the Newborn, Arch. Dis. Childhood **18**:161, 1943.

122. Gimson, J. D.: Haemolytic Disease of the Newborn (Erythroblastosis Foetalis): Its Treatment with Rhesus-Negative Blood, Brit. M. J. **2**:293, 1943.

123. Lloyd, T. W.: The Rh Factor in Haemolytic Anaemia of the Newborn, Brit. M. J. **1**:132, 1943.

124. Gallagher, F. W.; Danis, P. G., and Jones, L. R.: The Rh Factor in Relation to Jaundice of the Newborn Infant (Erythroblastosis Fetalis), J. Pediat. **22**:171, 1943.

125. Kariher, D. H., and Spindler, H. A.: Erythroblastosis Fetalis and the Blood Factor Rh, Am. J. M. Sc. **205**:369, 1943.

126. Dameshek, W.; Greenwalt, T. J., and Tat, R. J.: Erythroblastosis Foetalis (Acute Hemolytic Anemia of the Newborn): Preliminary Report, Am. J. Dis. Child. **65**:571 (April) 1943.

127. Reisner, E. H., Jr.: Morphology of Erythrocytes in Erythroblastosis Foetalis, Arch. Int. Med. **71**:230 (Feb.) 1943.

cytic peaks, was observed. In the remaining case the infant had a monophasic microcytic curve, consistent with the large number of microspherocytes observed in the blood film. In this case a transfusion of paternal blood had been followed by an increase in icterus, anemia and enlargement of the liver and spleen. The macrocytic peak observed in the other 23 cases of erythroblastosis could not be accounted for on the basis of the reticulocytosis alone. Differential counts made on the nucleated red cells of 6 patients with severe fatal erythroblastosis showed megaloblasts present in all films. The macrocytic peak encountered was suggested as resulting from a deficiency of the erythrocyte-maturing factor. Further support for this explanation was found at postmorten study, when in 4 of the infants studied the liver, the site of storage of the erythrocyte-maturing factor, proved to have varying degrees of hepatic injury, ranging from extensive hemorrhagic necrosis to invasion of the hepatic parenchyma by extramedullary hemopoiesis. Damage to the liver in animals following antigen-antibody reactions has been reported, although the author observes that it remains to be shown whether focal necrosis occurs in the livers of animals given a hemolytic antiserum. The possible role of hepatic damage in the production of a macrocytic blood picture in other hemolytic anemias in human beings is raised. Administration of liver extract as an adjunct to transfusions is suggested as rational therapy for these diseases.

Casey and Crowson [128] performed nucleated erythrocyte counts on the blood of 116 infants in whose cases the Rh group was known for both the mother and the child. For the 86 infants whose blood was compatible with that of the mother, with respect to the Rh factor, an average of 0.39 nucleated red blood cell per 10,000 erythrocytes was encountered. Of 24 infants whose blood was different from that of the mother, 7 had nucleated cell counts of over 2 per 10,000 erythrocytes. Counts of this height were found for only 9 of 92 infants whose blood showed Rh compatibility with that of the mother. The mortality among infants with nucleated counts over 5 per 10,000 was 67 per cent. Witebsky and Heide [129] found Rh antibodies in the breast milk of 2 mothers with erythroblastotic children. In one mother the Rh antibody titer of the serum on the fifth postpartum day was 1:256, while the titer in the milk of the first postpartum day was 1:16. In the other mother the titer of 1:8 was the same in the serum and in the colostrum. If it is assumed that the antibody passes through the infant's intestinal tract, breast milk would serve as a further stimulant to the hemolytic process in the child.

Case reports of interest include that of Fernandez Fuster,[130] who observed the first erythroblastotic child of a mother, born at her ninth pregnancy, and that of Kariher,[131] who reports a fatal instance of the disease in one of twins. The placentas were characteristic of a double ovum gestation; the father's blood was Rh positive; that of the mother, Rh negative. The affected twin had Rh-positive blood, while the surviving twin had Rh-negative blood, and the explanation for this difference lies in the assumption that the father is heterozygous, with the genotype Rhrh, and the mother is of Rh-negative phenotype, or of the genotype rhrh. In such circumstances 50 per cent of the offspring would be expected to be of Rh-positive phenotype (genotype Rhrh) and 50 per cent of Rh-negative phenotype (genotype rhrh). A similar situation was used by Race and his associates [132] to explain the birth of 3 healthy children after a child with Rh-positive blood had been delivered to a mother with Rh-negative blood, observed by Bentall.[133]

Some children with erythroblastosis were found with the Rh factor absent in both their blood and that that of their mothers. This situation was observed by Hertzog [134] and further study of the blood groups of the parents and the infant showed the blood of the father and that of the child to be of type B and that of the mother of type A. The mother's serum contained anti-B agglutinins in a dilution of 1 to 26.

Miller and Wilson [135] report the occurrence of macrosomia, cardiac hypertrophy, excessive erythropoiesis in the liver and hyperplasia of the islands of Langerhans in 3 of 18 infants born to diabetic mothers. It is pointed out that

128. Casey, A. E., and Crowson, S. H.: Nucleated Erythrocytes in Newly Born Infants in Relation to Maternal Rh Compatibility, Proc. Soc. Exper. Biol. & Med. **54**:321, 1943.

129. Witebsky, E., and Heide, A.: Further Investigations on the presence of Rh Antibodies in Breast Milk, Proc. Soc. Exper. Biol. & Med. **52**:280, 1943.

130. Fernandez Fuster, M.: The Rh Factor in the Etiology of Erythroblastosis Fetalis, Boll. Asoc. méd. de Puerto Rico **35**:313, 1943.

131. Kariher, D. H.: Erythroblastosis Fetalis (Hemolytic Disease of the Newborn) Occurring in One of Twins, J. A. M. A. **122**:943 (July 31) 1943.

132. Race, R. R.; Taylor, G. L.; Cappell, D. F., and McFarlane, M. N.: Significance of Rh Factor, Brit. M. J. **2**:690, 1943.

133. Bentall, A. P.: Significance of the Rh Factor, Brit. M. J. **2**:557, 1943.

134. Hertzog, A. J.: Problems Encountered in Explaining Certain Cases of Erythroblastosis Fetalis on the Rh Theory, Minnesota Med. **26**:1057, 1943.

135. Miller, H. C., and Wilson, H. M.: Macrosomia, Cardiac Hypertrophy, Erythroblastosis, and Hyperplasia of the Islands of Langerhans in Infants Born to Diabetic Mothers, J. Pediat. **23**:251, 1943.

the same anatomic abnormalities have been found in infants with erythroblastosis fetalis born to nondiabetic mothers. Despite the fact that all the diabetic mothers were proved to have Rh-positive blood, the possibility of some common factor in the causation of the two conditions is raised.

Race and his collaborators [136] in England present further evidence, from a second series of 129 families, comprising 348 children, that group A, A_2, B, O, and MN factors conform to the accepted genetic laws of inheritance. Boorman and Dodd,[137] by a technic based on the ability of a group-specific substance to inhibit specifically its corresponding antibody, offer evidence that M, N and Rh are, in contradistinction to the previous views, present in the tissues, although only in small amounts as compared with the concentration of A and B, and are detectable in the saliva and body fluids. If these findings are substantiated, a reconsideration of the theory of the causation of the hemolytic disease of the newborn is required. It has been supposed that the high incidence of erythroblastosis fetalis due to Rh incompatibility between the blood of the mother and that of the infant, as contrasted to the A, B and O groups, was due to the fact that maternal agglutinins ABO were absorbed by the infant's tissues and body fluids, whereas the Rh factor became promptly attached to the red cells. In the few instances in which erythroblastosis has been shown to be due to ABO incompatibility, it has been assumed that the infant was a "nonsecretor," without tissue antigen available to neutralize the maternal antibodies. This explanation is based on a misconception of the terms "secretor" and "nonsecretor," according to the authors. Both have group-specific substance in the tissues, but in the case of the "nonsecretors" the factor is insoluble in water. It is hypothesized that it is the soluble group-specific substances present in body fluids which serve primarily to neutralize maternal agglutinins. An insufficiency rather than an absence of the group-specific substance in erythroblastosis fetalis is assumed as responsible for the hemolytic disease of the newborn. Wiener and Belkin [138] demonstrated that the distinction between secretors and nonsecretors of group-specific substance in the saliva is just as evident in the newborn as in the adult.

Inheritance and Variants of the Rh Factor.—A record of 1,122 unselected blood donors in South Wales showing blood type and Rh reaction is given by Hoare.[139] The persons with Rh-positive blood made up 84.6 per cent of the series. Wiener, Sonn and Belkin [140] summarized their study on the heredity and distribution of the Rh factor in 83 white and 11 Negro families. Among the 274 children there was but 1 apparent exception to the predicted Rh type. In this case the supposed father's blood was found to belong to type N and the child's to type M, which was evidence that the child in question was illegitimate. The Rh factor is shown by Wiener and Sonn [141] to be inherited as a single mendelian dominant. An independent assortment of genes determining the Rh factor and blood types A. B, M and N was suggested from a study of 40 families with 138 children. Three varieties of anti-Rh agglutinins are discussed by Wiener [142] and by Wiener and Sonn.[143] Standard anti-Rh serum reacts with the blood of about 85 per cent of which persons; anti-Rh_1 serum gives about 70 per cent positive and anti-Rh_2 serum about 35 per cent positive reactions. Human serums combining the agglutinins anti-Rh and anti-Rh_1 are designated anti-Rh'. Anti-Rh and anti-Rh_2 combined serums are termed anti-Rh". By combining the three types of agglutinins five varieties of Rh agglutinogen are demonstrated, namely, Rh_1, Rh_2, Rh, Rh', Rh". If the Rh-negative blood is included, the five agglutinogens may be combined to form eight Rh blood groups. All but one of these types have been encountered, the type Rh'Rh". However, this is calculated to be present in an extremely low percentage of the population. The great majority of Rh-positive bloods belong to type Rh_1. Heredity studies by Wiener and Landsteiner [144] showed that Rh_1 and Rh_2 are both dominant over Rh; Rh_1 is dominant over Rh_2. A study by Levine and

136. Race, R. R.; Ikin, E. W.; Taylor, G. L., and Prior, A. M.: A Second Series of Families Examined in England for the A_1A_2BO and MN Blood Group Factors, Ann. Eugenics **11**:385, 1942.

137. Boorman, K. E., and Dodd, B. E.: The Group-Specific Substances, A, B, M, N, and Rh: Their Occurrence in Tissues and Body Fluids, J. Path. & Bact. **55**:329, 1943.

138. Wiener, A. S., and Belkin, R. B.: Group-Specific Substances in the Saliva of the Newborn, J. Immunol. **47**:467, 1943.

139. Hoare, E. D.: Occurrence of the Rh Antigen in the Population, Brit. M. J. **2**:297, 1943.

140. Wiener, A. S.; Sonn, E. B., and Belkin, R. B.: Heredity and Distribution of Rh Blood Types, Proc. Soc. Exper. Biol. & Med. **54**:238, 1943.

141. Wiener, A. S., and Sonn, E. B.: Heredity of the Rh Factor, J. Genetics **28**:155, 1943.

142. Wiener, A. S.: Genetic Theory of the Rh Blood Types, Proc Soc. Exper. Biol. & Med. **54**:307, 1943.

143. Wiener, A. S., and Sonn, E. B.: Additional Variants of the Rh Type Demonstrable with a Special Human Anti-Rh Serum, J. Immunol. **47**:461, 1943.

144. Wiener, A. S., and Landsteiner, K.: Heredity of Variants of the Rh Type, Proc. Soc. Exper. Biol. & Med. **53**:167, 1943.

Wong [145] of 150 Chinese persons residing in New York city showed that only one of this group had Rh-negative blood. Through the use of Rh_1 anti-serum, the incidence of Rh-negative blood in the yellow race was twenty-one times less frequent than in the white race. From a search of the literature a corresponding scarcity was found of reported cases of erythroblastosis in Chinese infants.

Sickle Cell Anemia.—Cases of active sickle cell anemia in 2 different white families are reported by Ogden.[146] Both mothers and 5 siblings were shown to have the sickling trait. In one family, of German descent, the great-great grandfather was a Negro, while in the other family, of Spanish descent, no Negro admixture could be traced. The 2 families are the first of Spanish and German ancestry reported as having the sickling trait. It is the author's unqualified opinion that the sickling trait in a white person is a definite proof of admixture of Negro blood in the immediate or remote ancestry. He examined 910 white persons, admitted to the outpatient department of a New Orleans hospital, for the sickling trait with a moist whole blood preparation. No sickling was encountered when the films were examined by the method of Emmel. Six hundred and ninety-two Negroes were similarly examined. Forty-five (6.5 per cent) showed sickling, and sickle cell anemia was encountered in 7 (1 per cent). Mera [147] has made some preliminary studies of the incidence of sickle cell anemia in Colombia. Four hundred and eighty-nine school children in one Colombian town with a Negro population of 80 per cent were examined, and 5.5 per cent were shown to have the sickle cell trait and 4 per cent sickle cell anemia.

Greenwald and associates [148] reported a case of sickle cell anemia in a 54 year old white woman in whom a metastatic carcinoma was found at postmortem examination. The patient, an adopted child, came from a village in Italy where Negroes were unknown. Ten of 12 available descendants of the patient were examined, and the sickling trait was found in 3 of the 6 living children and in 1 grandson. Eighteen other instances of sickle cell anemia in white persons gathered from the literature are presented. Bull [149] discusses the case of a 22 year old Indian woman who exhibited the traits generally associated with sickle cell anemia. Although 16 members of the patient's family were examined, no other instance of the disease could be found in the family. Admixture of Negro blood was not evident in the family history.

Stasney [150] describes the pathologic changes observed in a case of sickle cell anemia in which an unusual degree of erythrophagocytosis occurred in the liver and hemosiderosis was seen in the spleen. The liver was distended with enlarged Kupffer cells containing many sickle-shaped erythrocytes. In the spleen increased connective tissue and hyperactive Kupffer cells were noted. Twelve cases studied from the necropsy record and 13 others garnered from the literature were tabulated as to the size of the liver and spleen and the degree of erythrophagocytosis and hemosiderosis in these organs. Erythrophagocytosis was found to vary widely, with the Kupffer cells of the liver being most frequently involved.

The effect of breathing 80 to 100 per cent oxygen on the erythrocyte equilibrium in 3 patients with sickle cell anemia is reported by Reinhard and his associates.[151] It was thought that a reduction of the rate of hemolysis and a relief of pain during crisis might possibly result. Oxygen was administered without intermission for eight to twenty days, and, although relief from muscular or abdominal pain did not regularly result, a prompt fall in the number of sickle cells in both the arterial and the venous blood occurred. Excretion of urobilin was not altered sufficiently to indicate that the rate of hemolysis had been changed. After four to six days of therapy a decline in the reticulocytosis occurred, followed by a drop in the red cell count amounting to 500,000 to 1,500,000 cells per cubic millimeter. A sharp reticulocytosis and rise in the erythrocyte level to the pretreatment level followed discontinuation of oxygen therapy. It is suggested that administration of approximately 100 per cent oxygen depressed erythropoiesis and was in effect the physiologic opposite from

145. Levine, P., and Wong, H.: The Incidence of the Rh Factor and Erythroblastosis Fetalis in the Chinese, Am. J. Obst. & Gynec. **45**:832, 1943.

146. Ogden, M. A.: Sickle Cell Anemia in the White Race with Report of Cases in Two Families, Arch. Int. Med. **71**:164 (Feb.) 1943.

147. Mera, B.: Preliminaryes del estudio de la meniscocitemia en Colombia, South America, Bol. Ofic. san. panam. **22**:680, 1943.

148. Greenwald, L.; Spielholz, J. B., and Litwins, J.: Sickling Trait in a White Adult Associated with Hemolytic Anemia, Endocarditis and Malignancy, Am. J. M. Sc. **206**:158, 1943.

149. Bull, G. M.: A Case of Sickle Cell Anaemia in an Indian Woman, Clin. Proc. **2**:147, 1943.

150. Stasney, J.: Erythrophagocytosis and Hemosiderosis in the Liver and Spleen in Sickle Cell Disease, Am. J. Path. **19**:225, 1943.

151. Reinhard, E. H.; Moore, C. V.; Dubach, R., and Wade, L. J.: Effect of Breathing 80 to 100 per cent Oxygen on the Erythrocyte Equilibrium in Patients with Sickle Cell Anemia, J. A. M. A. **121**:1245 (April 10) 1943.

erythroid stimulation encountered with low oxygen tension. No toxic manifestations other than inflammation and congestion of the mucous membranes of the upper respiratory tract were found.

Helm and Jacobs [152] demonstrated that the erythrocytes of Negroes resisted hemolysis in solutions of thiourea to a greater degree than those of members of the white race. Differences were also noted when the red cells were suspended in acidified solution of sodium chloride. In 1 patient with sickle cell anemia a similar but exaggerated resistance to hemolysis was recorded. The observed alterations were attributed in part to a higher osmotic resistance of some erythrocytes present in Negro blood.

Mediterranean "Target Cell" Anemia.—Smith [153] examined 63 persons from 16 families exhibiting Mediterranean anemia and reached the conclusion that a mild form of this disease is prevalent. Fifty-four of the 63 persons revealed abnormalities in the blood, including anisocytosis, poikilocytosis, basophilic stippling and increased resistance of erythrocytes to hypotonic solutions of sodium chloride. Severe anemia was present in 12 subjects, all children. The recognition of the milder forms of this disorder depended on the abnormalities just noted and on varying degrees of hypochromic anemia, occasionally polcythemia, an elevated icterus index and the presence of "target" cells, reticulocytes and macrocytes. Hypochromic and polychromatophilic macrocytes were common, and their presence among cells which were predominantly microcytic was an important diagnostic feature. The observation of flattened or oval red cells of normal size, together with the other morphologic changes, which were out of proportion to the degree of anemia, is given as a cardinal principle in the diagnosis. Target cells occurred in but half of the blood films examined, despite an increased resistance to hypotonic sodium chloride solution in all but 1 instance. Microscopic examination of the sediment from the solution used in the fragility tests failed to reveal bowl-shaped cells, considered to be the forerunners of target cells. The author does not regard the target cell as a specific characteristic of Mediterranean anemia but believes that the fundamental defect resides in an abnormal thinness and flatness of the erythrocyte. This quality is reflected in the appearance of the erythrocytes in fresh as well as in stained films and in their resistance to hypotonic solutions. Persons with slight abnormalities of the blood appeared healthy and did not exhibit splenomegaly. Included in this group were the parents of children with severe forms of the disease. The genealogic distribution of this trait led to the conclusion that Mediterranean anemia is transmitted as a dominant characteristic.

Rohr [154] reports a Swiss family manifesting hemolytic, hypochromic anemia with the characteristic blood and skeletal changes of Mediterranean anemia, although admixture with Italian or Mediterranean peoples could not be traced. The mother, a daughter and a son were affected. Izzo, Ferradas and Porto [155] describe 3 brothers suffering from this disorder. Roentgenologic evidences of the disease were seen in the skull and metacarpal bones in 2, and the third brother showed the disease only in a benign, subclinical form. Van Ravenswaay, Schnepp and Moore [156] remark that the chills, fever and splenomegaly which are an intimate aspect of familial erythroblastic anemia have led to confusion with chronic malaria, particularly in the Mediterranean area, where both disorders are prevalent. Cooley's anemia should be readily distinguished from malaria by its inherited characteristics, the morphologic appearance of the red cells, icterus, varying degrees of anemia, skeletal changes and mongoloid facies. The primitive forms of treatment experienced by the patient whose case is reported included frequent bleeding by suction cups and external pressure on the spleen. The authors comment that until more is known concerning the supposed faulty metabolism of hemoglobin in this disease, no more certain therapeutic regimen is at hand to replace these crude measures.

Twenty-two patients with postvaccinal (yellow fever) jaundice admitted to an army base hospital were shown by Greenblatt and Kaplan [157] to have a high percentage of target cells in their blood films. No exception was found, although

152. Helm, J. D., and Jacobs, M. H.: Some Apparent Differences Between the Erythrocytes of White and Negro Subjects, J. Cell. & Comp. Physiol. **22**:43, 1943.

153. Smith, C. H.: Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia: Diagnosis of the Trait, or Mild Form of the Disease, Am. J. Dis. Child. **65**:681 (May) 1943.

154. Rohr, K.: Familiäre hämolytische hypochrome Anämie (Anämie von Cooley Typus beim Erwachsenen), Helvet. med. acta **10**:31, 1943.

155. Izzo, R. A.; Ferradas, J. B., and Porto, J.: Anemia del Mediterraneo (anemia eritro-blastica de Cooley), Publ. d. Centro de invest. tisiol. **6**:343, 1942.

156. van Ravenswaay, A. C.; Schnepp, K. H., and Moore, C. V.: Familial Erythroblastic Anemia: Thalassemia—Cooley's Anemia; Notes on Its Primitive Treatment, J. A. M. A. **122**:83 (May 8) 1943.

157. Greenblatt, I. J., and Kaplan, G.: Target Cells in Postvaccinal Jaundice, J. A. M. A. **122**:806 (July 17) 1943.

no parallel could be drawn between the number of target cells present and the severity of the disease. An increased resistance of erythrocytes to hypotonic chloride solution was noted in 73 per cent of the cases.

HEMOGLOBINEMIA AND HEMOGLOBINURIA

Hoffman and Kracke [158] point out that hemoglobinuria should be regarded as a urinary manifestation of increased destruction of erythrocytes. The mechanism responsible for hemoglobinuria depends, first, on excessive intravascular destruction of red cells and, second, on the renal threshold of the pigment. The authors report a classification of the causes of hemoglobinuria essentially the same as that for the hemolytic anemias and divided into exogenous and endogenous causes. Chemical agents, such as the sulfonamide drugs and phenylhydrazine, and typhoid, scarlet fever and parasitic infections are examples of exogenous causes. Transfusion reactions, snake poisons, burns and "bay sickness," or Haff disease, seen in the vicinity of Königsberg, Germany, are further causes of this class. Endogenous causes include familial and acquired hemolytic anemia and sickle cell anemia.

Paroxysmal hemoglobinuria is seen after exposure to cold, after physical exertion (march hemoglobinuria) and after ingestion of the Fava bean in previously sensitized persons. Nocturnal hemoglobinuria (the Marchiafava-Micheli syndrome) is characterized by exacerbations of hemolysis occurring mainly at night. Paroxysmal cold hemoglobinuria is associated with an autohemolysin which attacks the erythrocytes after chilling. Posture has been stressed as a causative factor in march hemoglobinuria, while the initiating abnormality in the nocturnal form of the disease remains obscure.

Paralytic myoglobinuria, a rare condition in man which is characterized by passage of myoglobin rather than of hemoglobin, is associated with development of muscular dystrophies. Such a case is described by Bywaters and Dible,[159] who summarize the 7 published cases of this interesting condition. The disease is more commonly seen in horses, but when it occurs in human beings it is accompanied by the passage of black urine, fever, pain and swelling of the affected muscles. Subsequent muscular paralysis, with loss of tendon reflexes, and atrophy follow. In addition to myoglobin, the urine contains casts and an associated elevation of blood urea nitrogen is common. Myoglobinuria may also occur after severe injury to muscles and in the Haff disease. Exercise may precipitate an attack, and death in uremia may follow.

Smith and Evans [160] report preliminary studies which lead them to believe that the increased fragility of the erythrocytes observed in blackwater fever is related in part to a lowered p_H of the blood. Convincing proof for this relationship is not evident from their published observations. As Dacie and Murgatroyd [161] and Loutit [162] point out in letters to the *British Medical Journal* commenting on this report, the causal relationship between fragility in vitro and hemolysis in vivo is itself open to debate. Foy and Kondi [163] demonstrated that erythrocytes from patients with blackwater fever are abnormally susceptible to hemolysis in solutions of lysolecithin.

Paroxysmal Nocturnal Hemoglobinuria.—Dacie and Firth [164] administered 2,000 cc. of stored human serum over a twelve day period to a subject with paroxysmal nocturnal hemoglobinuria. A prompt exacerbation of hemoglobinuria occurred after each infusion, but at the completion of this therapy the urine remained free of abnormal pigment for ten days. Despite the alteration in excretion of hemoglobin, the erythrocyte and hemoglobin values of the blood were not raised. A 500 cc. transfusion of a concentrated suspension of red cells given at the end of the ten day period caused a hemolytic episode marked by intense hemoglobinuria within forty-eight hours. Differential agglutination of the patient's cells after transfusion revealed that the donor's cells survived normally despite a fall in the total erythrocyte count. Not only did the observation indicate great destruction of the patient's own cells, but the survival of the donor's cells substantiated the theory that the apparent abnormality in this disorder lies in the red cells. The patient's erythrocytes were seen to increase in their resistance to in vitro lysis following transfusion, this alteration persisting for about one week. Hemoglobinuria disappeared after

158. Hoffman, B. J., and Kracke, R. R.: Hemoglobinuria, Clinics **2**:179, 1943.

159. Bywaters, E. G. L., and Dible, J. H.: Acute Paralytic Myohemoglobinuria in Man, J. Path. & Bact. **55**:7, 1943.

160. Smith, F., and Evans, R. W.: Effect of the p_H of the Blood on Haemolysis with Special Reference to Blackwater Fever, Brit. M. J. **1**:279, 1943.

161. Dacie, J. V., and Murgatroyd, F.: Effect of p_H of Blood on Haemolysis, Brit. M. J. **1**:458, 1943.

162. Loutit, J. F.: Blood p_H and Haemolysis, Brit. M. J. **1**:360, 1943.

163. Foy, H., and Kondi, A.: Lyso-Lecithin Fragility in Blackwater Fever and Haemolytic Jaundice, Tr. Roy. Soc. Trop. Med. & Hyg. **37**:1, 1943.

164. Dacie, J. V., and Firth, D.: Blood Transfusion in Nocturnal Haemoglobinuria, Brit. M. J. **1**:626, 1943.

the hemolytic transfusion reaction and did not recur until the erythrocyte level six weeks later had regained the pretransfusion value.

Chronic hemolytic anemia in a 5½ year old white boy marked by paroxysmal nocturnal hemoglobinuria is reported by Pierce and Aldrich.[165] It is the first time this disorder has been mentioned as occurring in a patient under 17 years of age. Attacks of abdominal pain, icterus, anemia and purpura characterized the illness, together with hemoglobinuria and an increased fragility of the erythrocytes in acidified serum. Splenectomy, performed for the thrombopenia before the diagnosis was apparent, failed to alter the hemolytic aspect of the illness, although the platelet counts improved.

Hoffman and Kracke[166] describe their observations on the p_H of blood of a patient with nocturnal hemoglobinuria, determined on the patient's awakening and again during the day, and also similar observations on control subjects. Sleep was invariably followed by hemoglobinuria in the affected subject, and altering the sleeping habits from nocturnal to daylight hours again produced dark black urine during somnolence. The administration of epinephrine base in oil and of an aqueous extract of the adrenal cortex (eschatin) arrested the hemoglobinuria, but it recurred promptly when the medication was withdrawn. Synthetic epinephrine bitartrate, and desoxycorticosterone were without effect on excretion of hemoglobin. Parasympathetic stimulants caused the urine to clear if neostigmine and pilocarpine hydrochloride were used. After administration of the latter drug a twenty day period elapsed before the urine voided after sleep again showed its characteristic dark color. The degree of anemia and the reticulocytosis were not altered by remissions of hemoglobinuria produced by any of these agents. It was concluded that decreasing the nocturnal hemoglobinuria failed to alter the underlying disease process.

Dacie and Richardson[167] studied the fragility of erythrocytes from 2 patients with chronic hemolytic anemia and nocturnal hemoglobinuria. Defibrinated serum adjusted to a p_H range of 6.0 to 8.5 was used as the suspension medium. With the addition of guinea pigs' complement maximum hemolysis occurred at about p_H 7.2. A progressive increase in hemolysis was not observed with a decreasing p_H, for hemolysis was inhibited below p_H 6 and above p_H 8. Heilmeyer,[168] however, in a case he observed, reported an increased fragility of erythrocytes in an acid medium.

Abicht, Kuhlmann and Denks[169] noted a patient with a diurnal hemoglobinuria which occurred in the middle of the night and again in the morning. Confining the patient in a dark room failed to alter the time of appearance of the dark pigment in the urine. Shimizu[170] studied erythrophagocytosis in persons with paroxysmal hemoglobinuria. This phenomenon was accelerated by chilling the serum and destroyed by heating it to 52 C. for thirty minutes.

March Hemoglobinuria.—Gilligan, Altschule and Katersky[171] undertook to determine if intravascular hemolysis giving rise to hemoglobinemia, and at times hemoglobinuria, occurred with sufficient frequency after strenuous exercise to be considered a physiologic event. Cross country runners, ranging from 17 to 65 years of age, were studied when they were competing at distances of 2½ miles (4 kilometers) up to the marathon of 26 miles (41.8 kilometers). Hemoglobinemia was encountered in 5 of 11 runners after a race of 2.6 to 2.8 miles (4.2 to 4.5 kilometers) and in 5 of 11 who ran 4.5 to 5.1 miles (7.2 to 8.2 kilometers). Of 22 athletes who finished the 26.2 mile (42.2 kilometer) marathon, 18 had elevated plasma hemoglobin values. Hemoglobinuria was observed in 1 person on three separate occasions after a 5 mile (8 kilometer) race and in 4 of the 22 athletes at the end of the marathon. Both hemoglobinemia and hemoglobinuria disappeared rapidly after exercise was stopped, and their production was, therefore, considered a benign physiologic process resulting from sustained strenuous exertion and comparable to the albuminuria of exercise.

165. Pierce, P. P., and Aldrich, C. A.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Micheli Syndrome), J. Pediat. **22**:30, 1943.

166. Hoffman, B. J., and Kracke, R. R.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria: Case Report with Experimental Studies, J. Lab. & Clin. Med. **28**:817, 1943.

167. Dacie, J. V., and Richardson, N.: The Influence of p_H on in Vitro Haemolysis in Nocturnal Haemoglobinuria, J. Path. & Bact. **60**:375, 1943.

168. Heilmeyer, L.: Nachtliche Hämoglobinurie (Marchiafava-Anamie), Klin. Wchnschr. **22**:307, 1943.

169. Abicht, L.; Kuhlmann, F., and Denks, H.: Kasuistisher Beitrag zur Marchiafava-Michelischen Hämoglobinuria, Deutsches Arch. f. klin. Med. **190**:156, 1942.

170. Shimizu, G.: Studies on Erythrophagocytosis: Erythrophagocytosis in Paroxysmal Hemoglobinuria, Far East Sc. Bull. **2**:13, 1942.

171. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Physiological Intravascular Hemolysis of Exercise: Hemoglobinemia and Hemoglobinuria Following Cross-Country Runs, J. Clin. Investigation **22**: 859, 1943.

Methemoglobinemia.—The occurrence of familial idiopathic methemoglobinemia in 2 brothers is reported by Deeny, Murdock and Rogan.[172] This rare disease often has as its only symptom a permanent bluish discoloration of the skin which is usually present from birth. In the 2 brothers described, a deep blue hue was seen in the skin of the face, hands, feet, mucous membranes and, to a lesser extent, the trunk. The blood was a dark chocolate shade, and a spectroscopic examination revealed the presence of methemoglobin. Forty-three per cent of the hemoglobin was in the form of methemoglobin with the blood oxygen–combining capacity reduced to 13.2 volumes per hundred cubic centimeters of blood. Three hundred to four hundred milligrams of ascorbic acid daily was given orally to the 2 affected patients, with dramatic results. The methemoglobin fraction fell from 43 to 6 per cent; the blood oxygen–carrying capacity increased, and a striking improvement occurred in the color of the skin. After one year of observation both subjects continued free of skin discoloration. These observations confirm the 1939 report on the successful management of this syndrome with ascorbic acid.

Methemoglobin may appear in the blood after ingestion of acetanilid, antipyrine and acetophenetidin or as a result of anaerobic bacterial or malarial infection. Lester[173] studied the formation of methemoglobin after the oral administration of acetanilid and acetophenetidin and observed a cumulative effect only in the case of acetophenetidin. Petersen[174] produced methemoglobinemia experimentally in cats by the subcutaneous administration of orthoaminophenol and of nitrosobenzene. Heubner[175] believes that Heinz bodies, highly refractile bodies seen within erythrocytes, are not identical with the pigments of methemoglobin and sulfhemoglobin although they may appear after the administration of certain poisons.

EXPERIMENTAL STUDIES ON HEMOLYSIS

During the year 1943 a great variety of experimental studies concerned with the hemolysis of the erythrocyte were published.

Shen, Ham and Fleming[176] studied 40 patients suffering second and third degree thermal burns received in the Cocoanut Grove fire disaster. Hemoglobinuria was observed in 11, and in these persons the burned area involved ranged from 15 to 65 per cent of the body area. Hemoglobinemia, with values between 65 and 216 mg. of hemoglobin per hundred cubic centimeters of plasma, was recorded for 8 persons within thirty-six hours after injury. In 1 instance spectroscopic examination of the plasma identified oxyhemoglobin and methemoglobin, and in several cases in which there was gross hemoglobinuria similar pigments were found in the urine. Fragmentation of erythrocytes with budding and spherocytic and microspherocytic forms was observed in the blood films of patients suffering moderately severe or extensive burns. These persons likewise manifested an increased fragility of the red cells in hypotonic sodium chloride solutions, and 7 had associated hemoglobinuria. Five others with hemoglobinuria showed a normal red cell fragility. No agglutinins were detected in the serum at the time when the erythrocyte fragility was altered. Heating human blood in vitro to temperatures between 51 and 65 C. was seen to produce similar changes in the structure of the erythrocytes: budlike projections, progressive fragmentation, spherocytosis and microspherocytosis. These alterations were independent of the duration of heating. In dogs hemoglobinemia and hemoglobinuria were produced by the intravenous administration of blood previously heated to 53 C. The conclusion was reached from these observations that thermal burns may destroy a considerable volume of erythrocytes by heating the cells at the site of the burn. The temperature reached at the burned area, the volume of the blood subjected to destruction and the duration of the destructive temperature will determine the incidence of hemoglobinemia, hemoglobinuria and azotemia or the absence of these complications.

Tsai, Chen and Chiu[177] investigated the production of increased fragility by stasis in the erythrocytes of dogs' blood. Their observations support the conclusion that the increased fragility of erythrocytes under conditions of stasis is due

172. Deeny, J.; Murdock, E. T., and Rogan, J. J.: Familial Idiopathic Methaemoglobinaemia with a Note on the Treatment of Two Cases with Ascorbic Acid, Brit. M. J. **1**:721, 1943.

173. Lester, D.: Formation of Methemoglobin: Repeated Administration of Acetanilide and Acetophenetidine, J. Pharmacol. & Exper. Therap. **77**:160, 1943.

174. Petersen, C.: Studien über Methämoglobinbildung; Ortho-Aminophenol und Nitrosobenzol, Arch. f. exper. Path. u. Pharmakol. **198**:675, 1941.

175. Heubner, W.: Heinzkörperchen und Blutfarbstoff, Klin. Wchnschr. **21**:520, 1942.

176. Shen, S. C.; Ham, T. H., and Fleming, E. M.: Studies on the Destruction of Red Blood Cells: Mechanism and Complications of Hemoglobinemia in Patients with Thermal Burns; Spherocytosis and Increased Osmotic Fragility of Red Blood Cells, New England J. Med. **229**:701, 1943.

177. Tsai, C.; Chen, C. J., and Chiu, K. Y.: Observations on the Various Factors Influencing the Increase of Erythrocytic Fragility Induced by Stasis, Am. J. Physiol. **138**:519, 1934.

to the accumulation of osmotically active metabolites in the interior of the cell, which cause an uptake of water by the cell, with a subsequent increase in size of the cell and the assumption of a more spherical form.

Loewy and his associates [178] followed the total bilirubin output in 7 dogs who were receiving a high fat diet. Two dogs had external and 5 had internal biliary fistulas. The bilirubin output proved to be significantly higher with a high fat diet than with a calorically equivalent low fat diet. It was concluded that destruction of erythrocytes proceeded at a faster rate with a high fat diet than with a low fat diet and that this was probably due to some hemolytic action of the chyle present during the period of rapid absorption of fat. Longini and Johnson [179] suspended dog's erythrocytes in dog's serum obtained after the animal had fasted and also after ingestion of fat. They found that the cells subjected to the hyperlipemic serum proved significantly more fragile when subsequently placed in hypotonic sodium chloride solutions. Parallel studies after high intakes of sugar and protein failed to show an alteration of behavior of the red cells in hypotonic mediums. The suggestion was ventured that a high fat diet may be related to the causation of certain hemolytic anemias. Freeman, Loewy and Johnson [180] estimated that in dogs the free fatty acids and soaps absorbed from the fat of a normal diet were responsible for the lytic destruction of from 8 to 35 per cent of the total daily red cell destruction. These figures were derived in part from changes observed in the daily excretion of bile pigment of dogs given sodium oleate intravenously. The bile was collected by cannulating the common bile duct after first ligating the cystic duct.

Gerber [181] found that erythrocytes from a patient with congenital hemolytic icterus contained less than the normal amount of cholesterol. No change in this abnormality followed splenectomy.

Gillespie [182] reported that the addition of lysolecithin to suspensions of human, sheep or rabbit erythrocytes did not change their resistance to salt solutions, despite an alteration of the cells to a spherical form. This is cited as evidence against the hypothesis that congenital hemolytic anemia is due to a pathologic exaggeration of the action of lysolecithin on erythrocytes trapped in the spleen and also against the hypothesis that all hemolytic anemias are produced on the basis of a circulating hemolysin. The spherocyte in hemolytic anemias, it is pointed out, is not a perfect spheroid body and obtains its name through an abnormal thickness. A true spheroid erythrocyte is produced by various lysins, such as lysolecithin, without altering the cell volume. This allows swelling of the cell to take place in hypotonic solutions to a degree comparable to normal erythrocytes.

Napier and Sen Gupta [183] gave monkeys anti-monkey-erythrocyte serum and produced a fulminating hemolytic anemia with hemoglobinuria. Many spherocytes appeared in the blood after each acute hemolytic crisis, which confirmed the earlier observations of others in similar experimental studies with guinea pigs. An increasing susceptibility of red cells to hemolysis in hypotonic sodium chloride solutions was evident, and the Price-Jones curve showed a pronounced shift to the left.

Tompkins [184] followed a series of rabbits which were given lecithin intravenously in amounts varying from 0.4 to 1 Gm. daily six days a week for periods as long as seventy-four days. A gradual progressive anemia with reticulocytosis ensued. Accelerated erythropoiesis in the marrow and extramedullary activity in the spleen pointed to a chronic hemolytic process. The fragility of the erythrocytes did not deviate from normal, despite a spreading base observed in the Price-Jones curve, a fall in the volume index and a rise in the icterus index. Pathologic study of the tissues revealed changes representative of a lipid storage disease, with splenomegaly characterized by massive infiltration of macrophages and congestion and constriction of the sinusoids. It was concluded that the hemolytic anemia observed was a result of the direct action of lecithin on the red cell to make it more subject to frag-

178. Loewy, A.; Freeman, L. W.; Marchello, A., and Johnson, V.: Increased Erythrocyte Destruction on a High Fat Diet, Am. J. Physiol. **138**:230, 1943.

179. Longini, J., and Johnson, V.: Increased Red Blood Cell Fragility After Fat Ingestion, Am. J. Physiol. **140**:349, 1943.

180. Freeman, W.; Loewy, A., and Johnson, V.: In Vivo Hemolysis Produced by Soap Injections, Am. J. Physiol. **140**:556, 1944.

181. Gerber, B. A.: The Significance of the Cholesterol Content of Red Cells in Hemolytic Icterus, Ztschr. f. Kinderh. **63**:625, 1943.

182. Gillespie, W. A.: The Influence of Lysolecithin and of Incubation on the Shape, Size and Fragility of Erythrocytes, Quart. J. Exper. Physiol. **32**:113, 1943.

183. Napier, L. E., and Sen Gupta, P. C.; Bhaduri, N. V., and Sekar, C. C.: Studies in Haemolysis, Indian J. M. Research **31**:75, 1943.

184. Tompkins, E. H.: Effects of Repeated Intravenous Injections of Lecithin in Rabbits, Arch. Path. **35**:695 (May) 1943.

mentation and phagocytosis during passage through the congested and compressed splenic sinusoids.

Wilbur and Collier [185] compared the hemolytic action of lysolecithin and saponin on rabbit erythrocytes. From their experiments they concluded that the two lytic agents have independent modes of action in initiating hemolysis.

Roy [186] compared the hemolytic activity of a variety of substances, such as saponin, sodium oleate and cobra venom, and found no correlation between surface tension and the initiation of hemolysis. It was concluded that alterations in surface tension played only a secondary role in the production of hemolysis. Attention is called to the "Symposia on Quantitative Biology," [187] which contains a group of papers dealing with the fundamental problems in the permeability and the chemical composition of the erythrocyte.

Cormick [188] found that the fragility of infants' erythrocytes in hypotonic sodium chloride solutions did not differ appreciably from the values reported for cells of adults.

Roy [189] examined the blood of a variety of animals and found that the fragility of the erythrocytes varied inversely with the average cell diameter.

Maegraith and his associates [190] demonstrated that a variety of tissues exerted a lytic action on erythrocytes but that this action could be inhibited by heating the tissue to 80 C. before incubation with the test suspension of cells. This is taken as evidence that the lytic factor is probably enzymatic.

The inhibitory effect of plasma on hemolysis by saponin led Ponder [191] to believe that the fundamental reaction of lysis is an alteration in the permeability of the red cell membrane to hemoglobin, the lysin reacting with a component of the cell surface. Gupta and his associates [192] report that an infusion made from the leaves of Vitex peduncularis inhibits the in vitro hemolysis of saponins, acids, cobra venom and bile salts and increases the resistance of erythrocytes to hypotonic sodium chloride solutions. In hares similar observations were made after intramuscular injection of this material but no effect was noted when it was given orally.

Hemolysis of erythrocytes by exposure to light rays of the visible spectrum is reported by Meyerstein.[193] According to Leu, Wilbrandt and Liechti,[194] ultraviolet rays produce hemolysis by causing an osmotic alteration in the cell membrane. Bühlmann, Liechti and Wilbrandt [195] propose that roentgen rays hemolyze erythrocytes through denaturization of the cellular protein, a process that allows weak ions to gain access to the cell. Cerny, Liechti and Wilbrandt [196] explain the hemolysis of sheep erythrocytes by supersonic sound as a mechanical rather than an osmotic action.

The degree of in vitro hemolysis of erythrocytes by roentgen irradiation was found by Halberstaedter and Goldhaber [197] to depend on the nature of the suspension medium as well as on the concentration of cells. Dilute saline suspensions of the erythrocytes were resistant to hemolysis by x-rays. This led to the suggestion that irradiation may affect the red cells primarily through alterations in the suspending medium.

COLD HEMAGGLUTINATION

Stats and Wasserman [198] present a comprehesive review of cold hemagglutination, covering the serologic characteristics of this phenomenon and the clinical and laboratory attributes of this agglutinin, together with a bibliography listing 216 references. The term "cold agglutination"

185. Wilbur, K. M., and Collier, H. B.: Comparison of the Hemolytic Actions of Lysolecithin and Saponin, J. Cell. & Comp. Physiol. **22**:233, 1943.

186. Roy, A. C.: Surface Tension and Haemolysis, Indian J. M. Research **31**:109, 1943.

187. Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1940, vol. 8.

188. Cormick, J.: A Study of Quantitative Fragility Test in Children, Arch. Dis. Childhood **17**:227, 1942.

189. Roy, A. C.: On the Fragility of Erythrocytes in Hypotonic Saline, Indian J. M. Research **31**:103, 1943.

190. Maegraith, B. G.; Martin, N. H., and Findlay, G. M.: The Mechanism of Red Blood Cell Destruction, Brit. J. Exper. Path. **24**:58, 1943.

191. Ponder, E.: The Mechanism of the Inhibition of Hemolysis, J. Gen. Physiol. **27**:1, 1943.

192. Gupta, J. C.; Kahali, B. S., and Ganguly, S. C.: Vitex Peduncularis, an Anti-Haemolytic Agent, Indian M. Gaz. **77**:721, 1942.

193. Meyerstein, W.: Effect of Light on Red Blood Cells: The Light Sensitivity of Blood from Different Vertebrate Species, J. Physiol. **99**:510, 1940.

194. Leu, J.; Wilbrandt, W., and Liechti, A.: Untersuchungen über Strahlenhämolyse; ultra-violet Hämolyse, Strahlentherapie **71**:487, 1942.

195. Buhlmann, A.; Liechti, A., and Wilbrandt, W.: Untersuchungen über Strahlen-hämolyse; weiter Versuche über Röntgenhämolyse, Strahlentherapie **71**:285, 1942.

196. Cerny, A.; Liechti, A., and Wilbrandt, W.: Untersuchungen über Strahlenhämolyse; Hämolyse durch Ultraschall, Strahlentherapie **72**:202, 1942.

197. Halberstaedter, L., and Goldhaber, G.: Effect of X-Ray on Erythrocytes, Proc. Soc. Exper. Biol. & Med. **54**:270, 1943.

198. Stats, D., and Wasserman, L. R.: Cold Hemagglutination—An Interpretive Review, Medicine **22**:363, 1943.

is well chosen, for no other agglutinin depends so much on change in temperature for its activity. Its greatest effect is exhibited between 5 and 0 C. while at body temperatures, and usually at 25 C. or above, the agglutinin does not function. The presence of this attribute of certain serums is often first suspected when the blood taken in a red cell pipet is found grossly clumped. As the erythrocytes absorb cold agglutinins, clumping will occur when such cells are placed in anti-A and anti-B group typing serums and may lead to mistakes in blood group typing. The absorbed cold agglutinins will cause the erythrocytes to clump even in group AB serums which are without isoagglutinins, and similarly such serums will agglutinate group O cells devoid of agglutinogens. When such a phenomenon occurs at room temperatures, it may be apparent by the macroscopic appearance of the blood with evident clumping even along the barrel of the syringe. To guard against designating a person whose serum reacts in this way as of group AB, it is recommended that group AB results be checked by testing the patient's serum for isoagglutinins or by performing the grouping test at 37 C. In the presence of cold agglutinins, it is advisable to use erythrocytes washed three times in isotonic solution of sodium chloride at room temperature, or if unusually high titers are present, the washing should be doubled and performed with saline solution warmed to 37 C. If unwashed cells are used for grouping tests, the typing must be performed at 37 C., for at this temperature cold agglutinins, except in rare instances, are not active.

Clinically cold agglutinins are encountered in acute infectious diseases, including pneumonia, in particular the atypical type, staphylococcemia, scarlet fever, tonsillitis and occasionally some tropical diseases. The association of cold agglutinins in hemolytic anemia has long been noted. Owing to their irregular presence in this disorder and their persistence long after clinical cure of the hemolytic disease, there is considerable doubt as to the relationship, if any, between the hemolytic process and the agglutinins. The phenomenon of cold agglutination has been reported in association with pregnancy, and a further case is reported by the present authors. Cold agglutinins responsible for hemoglobinemia after chilling were likewise demonstrated. The similarity and differences between this disorder and paroxysmal cold hemoglobinuria of the syphilitic (Donath-Landsteiner) type are discussed, and, except for cold's activating the antibody, it is concluded that they bear little relationship. Cold agglutinins may play a part, it is felt, in the pathogenesis of the Raynaud syndrome. The normal peripheral vasoconstriction which follows chilling, according to this view, may be aggravated by hemagglutination within the constricted capillaries, so that further retardation or even complete cessation of blood flow is produced. Detailed experimental studies supporting this conclusion are reported elsewhere. In the experience of the authors, cold agglutinins have not led to transfusion reactions even when a titer of 1 to 1,024 has been encountered.

Precautions to keep the blood at approximate body temperature before transfusion are not thought necessary unless in vitro agglutination and hemolysis are evident at temperatures below 35 C. A detailed account is given of the laboratory technic employed in tests for cold agglutination and for agglutinin absorption. A Negro with symmetric gangrene of the tips of all four extremities was shown by Stats and Bullowa [199] to have cold agglutinins in his serum. A history of voiding dark urine after exposure to cold was volunteered, although subsequent experimental study failed to reproduce hemoglobinuria. The cold agglutination present was thought to be directly responsible for the gangrene. Unilateral hemoglobinemia following exposure of one forearm to cold was demonstrated in this person, as well as hemagglutination in the capillaries of the conjunctivas after irrigation of the conjunctival sac with iced solution of sodium chloride. Syphilis in an active form was ruled out by physical examination and negative serologic reactions of the blood and spinal fluid, although a history of a probable chancre was present. The Donath-Landsteiner test gave a negative result. Stratton [200] observed 5 persons with cold agglutinins: 1 with bronchiectasis, 1 with subacute bacterial endocarditis, 1 with carcinoma of the lung, 1 with carcinoma of the ileum and 1 with hemolytic anemia. The clinical syndrome of acrocyanosis associated with cold hemagglutination following an attack of atypical pneumonia was observed by Helwig and Freis.[201] It is their conclusion that intravascular agglutination was the underlying cause of the disorder.

The relation of cold agglutinins to atypical pneumonia received considerable attention during the past year, owing to the epidemic character

199. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities: Report of a Case, Arch. Int. Med. **72**:506 (Oct.) 1943.

200. Stratton, F.: Some Observations on Autohaemagglutination, Lancet **1**:613, 1943.

201. Helwig, F. C., and Freis, E. D.: Cold Autohemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, J. A. M. A. **123**:626 (Nov. 6) 1943.

of the latter disease. Turner and his associates [202] in England examined for the presence of cold agglutinins 219 serums taken from adult civilians and members of armed forces of Great Britain and the United States. Of 83 unselected patients with atypical pneumonia more than one half had a positive agglutinin titer of 1 to 32, while the serums of 23 showed titers of 1 to 128 or beyond. Of the control group of 132 patients suffering a variety of respiratory diseases, in only 5 did the titer exceed the normal level of 1 to 16. Further analysis of the patients for whom a diagnosis of atypical pneumonia was acceptable after careful examination showed that the cold agglutinin titer reached its peak between the tenth and the twentieth day of the illness but had no apparent relationship to the severity of the disease, therapy with sulfonamide compounds or the presence in the sputum of bacterial pathogens. Horstmann and Tatlock [203] also found cold agglutinins in 8 of 9 patients following atypical pneumonia when the serum was tested soon after withdrawal of blood. Few of the serums gave positive reactions when stored for appreciable periods. Autoagglutination at room temperature was observed in all of 54 members of Royal Indian Army troops suffering atypical pneumonia who were seen by Shone and Passmore.[204]

Dameshek [205] reported 3 instances of severe hemolytic reactions in patients with acute infectious diseases to whom sulfadiazine or sulfathiazole or both had been administered. Cold agglutinins in high titer were present in all; in vitro hemolysis at refrigerator temperature was present in 1; the underlying infectious process was atypical pneumonia in 2 and infectious mononucleosis in another. It was suggested that the treatment with sulfonamide compounds and the agglutinins might both be related to the observed hemolytic anemia, hemoglobinemia and hemoglobinuria. Three patients were encountered by Peterson, Ham and Finland [206] in whom an acute hemolytic anemia occurred during an attack of atypical pneumonia. Nickum [207] encountered cold agglutinins in the serum of a patient reportedly suffering with bronchial pneumonia. An instance of hemolysis was observed by Stats [208] when erythrocytes were placed in a serum containing a cold agglutinin in a titer of 1 to 20,000 if the cell suspension was first incubated at 4 C. and then gently tapped twenty times every five minutes. No hemolysis occurred if serum was used with a titer of 1 to 2,000 or if the red cell suspension was diluted. It is pointed out that this is an unusual phenomenon, requiring as it does cellular damage, supplied by the shaking, but occurring without the addition of complement.

The differential points between the three types of aggregations of erythrocytes are listed by Barnard.[209] Rouleau formation is a reversible reaction with the cell aggregates forming by opposition and depending on a physical mechanism. Pseudoagglutination is produced by a chemical change of the erythrocyte envelope allowing the cells to adhere in a bidimensional mass. This reaction may proceed to lysis of the cells. Hemagglutination is an immunologic mechanism, irreversible and causing erythrocyte hemolysis. The cell aggregates are tridimensional. Study of stored blood bank blood showed a direct relationship to exist between the degree of pseudoagglutination and hemolysis. A high incidence of severe hemolytic transfusion reactions was observed after the use of specimens with pseudoagglutinated cells but grossly free of hemolysis. The conclusion is drawn that pseudoagglutination is a precursor to, or a manifestation of, the initial stages of hemolysis by lipolytic agents and that stored blood showing such cell masses is not suitable for transfusion. Lack [210] made an interesting observation in the course of his studies on malaria infection in canaries. Direct visualization of circulating erythrocytes in the web of the foot showed progressive agglutination with increasing parasitic infestation until inter-

202. Turner, J. C.; Nisnewitz, S.; Jackson, E. B., and Berney, R.: Relation of Cold Agglutinins to Atypical Pneumonia, Lancet **1**:765, 1943; Development of Cold Agglutinins in Atypical Pneumonia, Nature, London **151**:419, 1943.

203. Horstmann, D. M., and Tatlock, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, J. A. M. A. **122**:369 (June 5) 1943.

204. Shone, S., and Passmore, R.: Pneumonitis Associated with Autohemagglutination, Lancet **2**:445, 1943.

205. Dameshek, W.: Cold Hemagglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, J. A. M. A. **123**:77 (Sept. 11) 1943.

206. Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167, 1943.

207. Nickum, J. S.: A Case of Cold Agglutination of Own Serum Treated by Heparin Intravenously, Connecticut M. J. **7**:475, 1943.

208. Stats, D.: Cold Agglutinated Erythrocytes: Hemolytic Effect of Shaking, Proc. Soc. Exper. Biol. & Med. **54**:305, 1943.

209. Barnard, R. D.: The Significance of Erythrocytic Pseudoagglutination, J. Lab. & Clin. Med. **28**: 1568, 1943.

210. Lack, A. R., Jr.: The Occurrence of Intravascular Agglutinations in Avian Malaria, Science **96**: 520, 1942.

ference with circulation resulted in permanent thromboses.

APLASTIC AND REFRACTORY ANEMIAS

Extensive consideration is given to the refractory anemias in three publications by Davidson, Davis and Innes in the *Edinburgh Medical Journal*, which deserve the careful perusal of all who are interested in this variety of anemia. The first contribution [211] deals with the technic of taking biopsy specimens by sternal puncture and the interpretation of such specimens and with the classification of the refractory anemias. The authors describe their technic and conclude that sternal puncture is the most satisfactory procedure available for the routine investigation of the bone marrow in clinical practice. They consider that it has at least two limitations, as follows: First, such an examination is of significance only if the sample is representative of the marrow as a whole; second, the sternal puncture technic is inadequate in cases in which it is desirable to preserve intact the histologic relationship of the formed elements of the marrow. The authors discuss adequately the nomenclature of marrow cells, and the reader who is interested should consult this comprehensive and authoritative description in the original. Although they consider that sternal puncture provides an invaluable aid in the diagnosis of the refractory anemias, it is emphasized that for its adequate interpretation it is essential that it be supplemented by a careful examination of the peripheral blood. Their classification of the refractory anemias, on the basis of cytologic changes in the bone marrow, as revealed by a study of the material obtained by sternal puncture, is as follows:

Refractory Anaemias

1. *With hypocellular, normoblastic marrow.*
   (*a*) Secondary to exposure to toxic substances. . . .
   (*b*) Idiopathic, of unknown origin.
      (i) Progressive hypoplastic anaemia with fatal termination. . . .
      (ii) Chronic hypoplastic anaemia, patients surviving two or more years. . . .
      (iii) Relapsing hypoplastic anaemia. . . .
2. *With hypercellular, megaloblastic marrow.*
   (*a*) Occurring in pregnancy and puerperium. . . .
   (*b*) Idiopathic. . . .
3. *With cellular, normoblastic marrow and arrested myelocyte maturation.* . . .

The second paper by these authors [212] is concerned with a discussion of the refractory anemias with a hypocellular, normoblastic marrow. This division is considered under two subgroups, namely, (*a*) those following exposure to toxic substances and (*b*) those of idiopathic type. There were 4 cases of the first group. In 1 case the anemia followed therapeutic administration of arsenic, and in another it developed after gold salts had been given in the treatment of rheumatoid arthritis. In both instances recovery occurred. In the other 2 cases the anemia was due to benzene and to trinitrotoluene poisoning respectively. In both of these cases the patient died. Both of the latter cases presented points of special interest. In the first, after the exposure to benzene fumes which caused aplastic anemia, lobar pneumonia developed, associated with leukocytosis and the blood picture of myelogenous leukemia. Furthermore, at necropsy a myeloid infiltration was found in the liver and spleen and the general pathologic picture was consistent with a diagnosis of myeloid leukemia. In the case in which nonfatal aplastic anemia developed as a result of injections of a gold compound, it is of interest that the patient's sister had likewise suffered from rheumatoid arthritis, which also had been treated with injections of a gold compound. In her case aplastic anemia likewise developed and terminated fatally. In 12 cases with a hypocellular, normoblastic picture in the bone marrow the anemia was classified as idiopathic. In 9 the anemia was progressive and proved fatal within a few months (average, seven). Three patients have survived for periods exceeding two years, and in 1 of these the condition has pursued a relapsing course which presented unusual features. No plausible explanation for the relapses or remissions was apparent to the authors. The outlook for these 3 patients is poor, though the one with the relapsing type appears to be in reasonably good condition despite a moderately severe anemia.

The third communication [213] by Davidson, Davis and Innes is concerned with cases of refractory anemia in which a cellular marrow is revealed by sternal puncture. In the cases associated with pregnancy there was severe anemia, with hemoglobin readings ranging from 17 to 52 per cent and a megaloblastic reaction of the bone marrow. The patients displayed transient periods of refractoriness, varying from two weeks to four months, despite intensive parenteral treatment with liver extract supplemented by administration of iron and vitamin concentrates. In the majority of cases repeated blood transfusions

211. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Studies in Refractory Anaemia: I. The Technique and Interpretation of Sternal Puncture Biopsies; Classification, Edinburgh M. J. **50**:226, 1943.

212. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Studies in Refractory Anaemia: II. Anaemias with Hypocellular, Normoblastic Marrows, Edinburgh M. J. **50**:355, 1943.

213. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Studies in Refractory Anaemia: III. Refractory Anaemias with Cellular Marrow, Edinburgh M. J. **50**: 431, 1943.

were necessary for the maintenance of life during such periods. Eventually recovery occurred in all cases. In the remaining 6 cases of refractory anemia the condition was considered to be idiopathic. They had the following features in common. The peripheral blood pictures were essentially those of severe macrocytic anemia, and the sternal marrow when first observed showed megaloblastic erythropoiesis. The patients were refractory to treatment with parenteral liver extract for periods varying from four to ten weeks, but all eventually responded to such treatment, with a restoration of normal blood formation. Four of the patients had histamine-fast achlorhydria, while 2 had free hydrochloric acid in the gastric juice during fasting. The authors state that in some respects the anemia in this group of cases resembles achrestic anemia as described by Israels and Wilkinson.[214] The authors also include in their classification a chronic granulocytopenic condition, on the grounds that it represents anemia refractory to treatment of any kind. It is said to differ from the classic acute agranulocytosis in the chronic course, the coexistence of a moderately severe degree of anemia and the absence of exposure to leukocytotoxic agents. It is debatable whether this disease should be classified as chronic refractory hypoplastic anemia or, on account of the striking leukopenia present, as chronic idiopathic agranulocytosis. In the opinion of the authors of the article, it probably corresponds to the condition classified by Bomford and Rhoads as "refractory anemia with immature cellular marrow, or chronic granulocytopenia."

A fatal case of anemia of the aplastic type arising in the course of antisyphilitic therapy is recorded by Grech, Rhodes and Grunberg.[215] A woman aged 53 years received three injections of a double glucoside of arsphenamine (stabilarsan) for secondary syphilis in 1931, but treatment was discontinued on account of a generalized arsenical dermatitis. A few months later further treatments were given, apparently without untoward symptoms. After ten years she appeared for treatment with a paralysis of the left third nerve. Over an interval of three months she was given 3.15 Gm. of stabilarsan intravenously and 6 cc. of chlorophenol salicylate intramuscularly. The patient returned in about one month with all the clinical features of severe aplastic anemia, which terminated fatally about one month later. The diagnosis was confirmed by necropsy. In a summary of the hematologic complications of the arsenical therapy for syphilis, the authors state that they may be divided into three types: (1) thrombopenic, (2) granulocytopenic and (3) aplastic. Approximately 50 cases of anemia of the aplastic type following arsenical therapy have been described, and the authors now add another. This variety of anemia has been recorded as occurring in patients who have received either small or large doses of arsenic, and they express the view that the condition must be regarded as one of intolerance to the drug.

Two fatal cases of idiopathic aplastic anemia are reported by Sacks and Bloom[216] in which the following were some of the points of note: (1) complete absence of bleeding in 1 case in the presence of a low platelet count, as compared with bleeding in the other case in the presence of a higher platelet count, although still much below the bleeding level; (2) the absence of any ulceration in 1 case, although there were no granulocytes, and the presence of ulceration in the other case, although there were still some granulocytes in the circulating blood; (3) the high temperature of each patient during the illness.

By definition Macfarlane and Currie[217] characterize idiopathic aplastic anemia, strictly speaking, as an anemia due to some unknown cause in which there is a failure of production of erythrocytes as shown by examination of the circulating blood and the bone marrow. In other words, they imply that only the red blood cells are involved, as they state that in such cases only an "uncomplicated anemia" exists. According to them, however, the term is generally applied to the state in which there is a progressive diminution in the formation of those elements which develop in the bone marrow, namely, erythrocytes, granulocytes and thrombocytes. They suggest the name originated by Frank, "aleukia hemorrhagica," as suitable for this anemia. Another condition included by them in the group of aplastic anemias is the one in which the blood picture is typical but the bone marrow is crowded with proerythroblasts and early normoblasts. We should like to comment that the various types of anemia which they have described under the general name of aplastic anemia are perhaps best included in that rather loose group which have in common their failure

214. Israels, M. C. G., and Wilkinson, J. F.: Achrestic Anaemia, Quart. J. Med. **5**:69, 1936; New Observations on Aetiology and Prognosis of Achrestic Anaemia, ibid. **9**:163, 1940; Refractory Anaemia: Aetiology and Treatment, ibid. **10**:235, 1941.

215. Grech, J.; Rhodes, A. J., and Grunberg, A.: Acute Aplastic Anaemia Following Antisyphilitic Treatment, Edinburgh M. J. **50**:65, 1943.

216. Sacks, I., and Bloom, M.: Two Cases of Aplastic Anemia, South African M. J. **16**:437, 1942.

217. Macfarlane, J. W., and Currie, J. P.: Idiopathic Aplastic Anaemia, Edinburgh M. J. **50**:171, 1943.

to respond to any known type of therapy and hence have been called the "refractory anemias." Of the 4 cases described in the article, 3 appear to be of the aplastic type and the fourth, as the authors suggest, might have been regarded as a case of subleukemic leukemia.

The development of anemia in a 55 year old Negress after the administration of only 11 Gm. of sulfathiazole is reported by Strauss.[218] The patient was known to have had hypertension for a number of years. Because of pronounced pyorrhea, all of the teeth were removed. After this a low grade fever developed, which was the indication given for the administration of the sulfathiazole. Eight days after the use of the drug had been discontinued, it was found that the hemoglobin content was 3.0 Gm. per hundred cubic centimeters and the red blood cell count 1,360,000 per cubic millimeter. The bone marrow films from aspirated sternal marrow showed a striking reduction in the number of nucleated red blood cells. A diagnosis of acute aplasia of the red blood cell-forming elements was made. It was considered that the patient had suffered from a toxic destruction of bone marrow cells involving the red blood cells exclusively. After removal of the drug, the symptoms slowly subsided and the bone marrow returned to normal activity. The patient made a slow but steady recovery.

The bone marrow findings in an unusual form of anemia are presented in considerable detail by Moeschlin and Rohr.[219] The marrow revealed complete absence of erythroblasts. The patient, a 20 year old white woman, was suffering with polyarthritis and an anemia which resisted all the usual therapeutic measures. Likewise the picture in the bone marrow remained unchanged. Erythroblasts were not found on repeated marrow punctures at various sites, including the sternum, hip bones and pelvis. The white cell elements were little altered except for a shift to the left of the young myeloid cells. No abnormality in the formation of platelets was observed. It is suggested that the faulty erythropoiesis, with absence of erythroblasts, may be analogous to agranulocytosis and aleukemic disturbances of the white cell elements. The patient was under observation for thirty months and required one hundred and twenty blood transfusions.

218. Strauss, A. M.: Erythrocyte Aplasia Following Sulfathiazole, Am. J. Clin. Path. **13**:231, 1943.

219. Moeschlin, S., and Rohr, K.: "Aplastische Anämie" mit jahr langen vollständigen Fehlen der Erythroblasten (Erythroblastophthise), Deutsches Arch. f. klin. Med. **190**:117, 1942.

(To Be Continued)

News and Comment

Open Meeting of New York Institute of Clinical Oral Pathology.—The New York Institute of Clinical Oral Pathology will hold its first open meeting at the New York Academy of Medicine on Monday evening, Oct. 30, 1944, in Hosack Hall. Outstanding investigators will participate in a symposium on "Fluorine and Dental Caries." Members of the medical, dental, public health and other professional groups are cordially invited. For further information address communications to the executive secretary of the institute, Mr. G. Roistacher, 101 East Seventy-Ninth Street, New York 21.

Officers of Chicago Society of Internal Medicine.—At the annual meeting of the Chicago Society of Internal Medicine, held May 22, 1944, the following officers were elected: president, Dr. Lee C. Gatewood; vice president, Dr. George E. Wakerlin, and secretary-treasurer, Dr. Howard L. Alt.

Book Reviews

Human Constitution in Clinical Medicine. By George Draper, M.D.; C. W. Dupertine, Ph.D., and J. L. Caughey Jr., M.D. Price, $4. Pp. 273. New York: Hoeber-Harper, 1944.

This small volume contains much that is familiar to many readers, for the authors have drawn freely on their previously published contributions in its preparation. The declared purpose of the book is to discuss for medical students the fact that there is an essential relationship between each individual person and the disease that he or she may have, that is, to stress the constitutional factor in disease; to quote the authors' repeated statement, it is "a study of the nature of the man within the patient." That the subject matter is of popular interest is evident by an early review which appeared in *Time*, entitled "Bodies Make a Difference."

The theory of constitution in relation to disease as presented herewith got its impetus from a series of observations made during the epidemic of infantile paralysis in 1916. Apparently, children who were victims of this epidemic possessed certain similar identifying qualities of physical form and general personality. This experience led to investigation of persons with other types of diseases.

The authors consider man so complex an organism that his totality can be approached only by a study of its component parts. Consequently, in their studies they have used as a plan the analogy of the four-paneled screen. The panels represent anatomy, physiology, immunity and psychology. Investigations directed to the factor of morphology were concerned with a combination of three methods: the anthropometric technic of Martin, the photographic somatotyping technic of Sheldon, and an over-all observation and correlation of feature, detail and relationship. The electrocardiograph and the spirometer were used chiefly for physiologic observations. The immunity phase was concerned with observations on infantile paralysis and acute rheumatic fever. In the psychologic method, no formal system or pattern of approach has been attempted. The psyche is regarded as the all-important and the most obscure component of the total animal. Admittedly, "the attempt to comprehend the interplay of forces registered upon each of the four panels of personality is obviously a cumbersome and timeconsuming occupation."

In chapter 8, which deals with anthropometry, is a record of detailed observations on 244 males and 585 females with various types of diseases. Common to both sexes are pernicious anemia, duodenal ulcer, acute rheumatic fever and cholecystic disease. In the diseases of males are included gastric ulcer and hypertrophy of the prostate gland, whereas the diseases of females include migraine, toxemia of pregnancy and carcinoma of the breast and the uterus. As this aspect of the research is an original and familial one, and perhaps based on less theoretic considerations, a few conclusions may be cited. Persons of linear design, in whom the gynic (female) component is moderate morphologically, have a tendency to have ulcer. Persons of a stocky, plump build, in whom the gynic emphasis is high, appear more often to be victims of disease of the gallbladder. The gallbladder type of male presents an aspect of massive softness, whereas the ulcer type of male is slender and hard. The morphologic characteristics of the pernicious anemia group suggest a eunuchoidal trend, because of the rather long legs, short faces, deep and short chests and broad pelves of affected persons. The victims of acute rheumatic fever are generally characterized by long faces and long trunks. The breadth of the shoulders and pelvis is also greater than the average; the thorax is broad and shallow but of large circumference. There is also a tendency for them to have fairly long arms and legs. Physical asymmetry, especially facial, may be present along with marked irregularity of the teeth and palate. The eyes are frequently out of line.

Conclusions with reference to the psychologic panel of the patient who has ulcer are familiar and interesting (pages 206 to 209) in view of current emphasis placed on the psychosomatic aspects and the growing realization of the importance of gastroduodenal ulcer and its equivalents in civilian and military medical practice.

Criticism is tempered by the authors' statement in the preface that there has been no attempt throughout the book to prove the position of human constitution in disease. Although the members of the medical profession are under great obligation to Draper and his co-workers for their exhaustive research, one cannot escape the conviction that their thesis has not been proved. The statistical technic is incomplete and faulty, and there is lack of correlative data pertaining to con-

trol groups in the different categories. Aside from the obvious cumbersome and time-consuming procedure, the knowledge of the immunologic, physiologic and psychologic phases is still so incomplete and so controversial in many respects that any conclusions drawn from panel studies must be taken with a grain of salt. Although the neuropsychiatric aspects of many human disorders are often grossly neglected by many practitioners and surgeons, an attitude which leads to erroneous diagnoses and harmful treatment, it seems that too much emphasis has been placed on the importance of the psyche by these authors. The concepts of the psychoanalysts, particularly those of the freudian school, leave the average well informed internist cold. There is always the risk of putting the cart before the horse. Many ulcer-bearing patients, for example, are obviously stable until the erroneous removal of a healthy gallbladder or appendix, or both, or a futile prolonged treatment on the basis of a diagnosis of psychoneurosis or irritable colon has provoked an anxiety neurosis or other disorder of personality because of the sudden realization that a cure has not been achieved, to say nothing of the long-drawn-out suffering, expense and loss of time from work. And, without any intention of belittling the importance of taking a complete history and making a thorough physical examination, the fact remains that objective methods of diagnosis in trained hands are increasingly accurate; in short, they usually are as accurate as an autopsy; therefore, these laborious studies in constitution do not assume the importance that some of its proponents would have one believe.

Technic of Electrotherapy and Its Physical and Physiological Basis. By Stafford L. Osborne, Ph.D., Assistant Professor of Physical Therapy, Northwestern University Medical School, and Harold J. Holmquest, B.S., Lecturer in Applied Physics, Northwestern University Medical School. Price, $7.50. Pp. XIX + 780, with index and 241 figures. Springfield, Ill.: Charles C Thomas, 1944.

This book does not make easy reading for the ordinary physician. It is divided into four main parts, dealing respectively with the medical implications of direct current, muscular stimulation by electricity, radiation and high frequency currents. Each of the chapters within these divisions begins with a description of what it is about, goes on to tell how such electrical methods as are mentioned should be used in treatment and ends with an outline of the results that may be expected from their proper employment. Considerable space is devoted to explaining as simply as possible the basic electrophysics and physiology of the technics involved, and in connection with this there are naturally a good many mathematical computations. At the end are two helpful appendixes which describe the use of logarithms and something of trigonometry.

A book of this character cannot be expected to have any great appeal to ordinary readers of general medical literature. Yet it is bound to be an extremely useful handbook for departments of physical therapy in hospitals and for physicians and medical students who are now commencing to wish for scientific and accurate information about a form of treatment which is rapidly becoming of increasing importance. The members of the medical profession are indebted to the two authors, neither of whom is a physician although both are concerned in the teaching of medicine and in the advancement of medical knowledge.

Psychiatry and the War. Edited by Frank N. Sladen, M.D., Physician in Chief, Henry Ford Hospital, Detroit. Price, $5. Pp. XXII + 505, with index. Springfield, Ill., Charles C Thomas, Publisher, 1942.

The McGregor Fund is an interesting fund, established in 1925 by an imaginative philanthropist and his wife. Two years ago the trustees of this fund decided to hold a three day conference on psychiatry and the war under its auspices as an educational project of great general interest and importance. This volume is the result.

The conference must have been most interesting to attend. A wide range of subject matter was covered, including discussions not only by psychiatrists but by psychologists, neurologists, surgeons and internists. The general purpose of each discusser was to consider the basic topic for which the meeting was called from his own viewpoint. There was a galaxy of stars.

The editor has been happy in presenting what was said in a manner easily understandable to physicians and medical students, or indeed to any one at all interested in this vast subject. One of those who was there wrote of the meeting: "The program was splendidly conceived, superbly executed. The conference was peculiarly fruitful in that it developed a rather complete perspective on psychiatry, coming out of the experience of a great many leaders." This volume gives to a wider audience the privilege of attending the conference, vicariously to be sure, but in an easy vehicle.

Functional Disorders of the Foot: Their Diagnosis and Treatment. By Frank D. Dickson and Rex L. Diveley. Second Edition. Price, $5. Pp. 352, with 202 illustrations. Philadelphia: J. B. Lippincott Company, 1944.

When the first edition appeared in 1939, "Functional Disorders of the Foot" promptly took its place on the working shelves of many physicians. The basic approach and the simple, practical solutions to commonly encountered disorders of the foot were readily appreciated.

The second edition offers a little more in the way of surgical procedure plus two new pertinent chapters. One of these, "Disorders of the Foot in Relation to Military Service," should prove most valuable all along the line, from induction center to rehabilitation camp. Some of this chapter is a condensation of information found elsewhere in the book.

The other new chapter, "Disorders of the Foot in Relation to Industry" emphasizes the importance of a complete health program for moderate-sized as well as for large plants. Here again are many practical parts regarding proper footwear and proper care of the feet.

Medical Diagnosis—Applied Physical Diagnosis. By Roscoe L. Pullen. Price, $10. Pp. 1106, with 583 figures. Philadelphia and London: W. B. Saunders Company, 1944.

This well and profusely illustrated treatise marks a decided advance over the conventional textbook on physical diagnosis. The entire scope of diagnostic methods is covered, as illustrated by chapter headings such as "Examination of Bones and Joints," "The Endocrine Survey" and "Practical Mental Measurements." It is of interest that the editor has called on no less than twenty-seven experts to write the chapters dealing

with different fields—an inarticulate confession of the complexity of modern medicine, which has practically eliminated the one man textbook. The book should be useful to the practitioner.

Practical Malaria Control. By Carl E. M. Gunther. Price, $2.50. Pp. 91. New York: Philosophical Library, Inc., 1944.

This small handbook is a practical outline dealing briefly but effectively with the commonest problems of control of malaria. It presents both phases, namely the epidemiologic measures required and the treatment of the individual patients. For physicians faced with the responsibility of control of this disease in a tropical environment this book will prove useful.

Collected Papers of The Mayo Clinic and The Mayo Foundation. Edited by Richard M. Hewitt, A. B. Nevling, John R. Miner, James R. Eckman and M. Katharine Smith. Volume XXXV, 1943. Price, $11. Pp. 875, with 208 illustrations. Philadelphia and London: W. B. Saunders Company, 1944.

The Mayo Clinic is to be congratulated on keeping up its fine output of original work in spite of the difficulties of war. One cannot review in detail the large number of papers or abstracts dealing with so many different problems; practically every field of clinical medicine is touched. A good index makes the material accessible to the systematic reader, and, as usual, the format and illustrations are outstanding.

Manual of Human Protozoa. By Richard R. Kudo. Price, $2. Pp. 125, with 29 plates. Springfield, Ill.: Charles C Thomas, Publisher, 1944.

Here in concise form and well illustrated are brief descriptions of the common "human protozoa." The book is beautifully printed on heavy paper and should be extremely useful, for quick reference, to both the physician and the medical student. There are chapters on technic and an index.

Principles and Practice of Inhalation Therapy. By Alvan L. Barach. Pp. 315, with 59 figures. Philadelphia, London and Montreal: J. B. Lippincott Company, 1944.

It seems highly appropriate that Dr. Barach, who has pioneered and labored so long in the field of inhalation therapy, should finally bring his experiences together in book form. By preparing this concise compendium he has done the practicing physician a real favor; it is indeed convenient to find between two covers the gist of matter fairly widely scattered in the literature. Theoretic questions, the rationale of clinical procedure and finally descriptions of apparatus and its use are all dealt with. The book is well printed and illustrated.